

# Gledište Hrvatskoga društva za hipertenziju o opaženom povećanom riziku za nastanak nemelanomskih karcinoma kože povezanom s liječenjem hidroklorotiazidom The Position of the Croatian So ...

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## Gledište Hrvatskoga društva za hipertenziju o opaženom povećanom riziku za nastanak nemelanomskih karcinoma kože povezanom s liječenjem hidroklorotiazidom

### The Position of the Croatian Society of Hypertension on the Observed Increase in Risk of Non-melanoma Skin Cancer Associated with Hydrochlorothiazide Treatment

Upravni odbor,  
Hrvatsko društvo  
za hipertenziju

The Governing  
Board of the  
Croatian Society  
of Hypertension

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Upravni odbor Hrvatskoga društva za hipertenziju na svojoj elektroničkoj sjednici održanoj 12. prosinca 2018. raspravljao je o opaženom povećanom riziku za nastanak nemelanomskih karcinoma kože povezanom s liječenjem hidroklorotiazidom i pripremio sljedeće mišljenje.

Europska medicinska agencija (EMA) poslala je 1. listopada 2018. upozorenje o opaženom povećanom riziku za nastanak nemelanomskih karcinoma kože povezanom s većim kumulativnim dozama hidroklorotiazida<sup>1</sup>. Njihova je preporuka da bolesnike treba upozoriti na rizik te da oni koji su na takvoj terapiji moraju redovito pregledavati kožu. Kao moguća preventivna mjera preporučuju se izbjegavanje izlaganja sunčanoj svjetlosti, ultraljubičastom (UV) zračenju i uporaba odgovarajuće zaštite. Nastavak liječenja hi-

The Governing Board of the Croatian Society of Hypertension held an e-meeting on December 12, 2018, where the observed increase in risk of non-melanoma skin cancer associated with hydrochlorothiazide treatment was discussed, and the following statement was prepared.

On October 1, 2018, the European Medicines Agency (EMA) published a warning on the increased risk of non-melanoma skin cancer associated with higher cumulative hydrochlorothiazide doses<sup>1</sup>. Their recommendation was to inform the patients of the risk and that patients receiving this treatment should undergo regular skin examinations. Other recommended preventive measures include avoiding exposure to sunlight, ultraviolet (UV) radiation, and the use of appropriate protection. Continued hydrochloro-

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## The Position of the Croatian Society of Hypertension on the Observed Increase in Risk of Non-melanoma Skin Cancer Associated with Hydrochlorothiazide Treatment

droklorotiazidom treba biti razmotren u bolesnika koji su već prije liječeni zbog nemelanomskog karcinoma kože.

Hrvatska agencija za lijekove i medicinske proizvode (HALMED) oglasila se svojim priopćenjem 22. studenoga 2018. kojim upozorava na malo povećan rizik od pojave nemelanomskog karcinoma kože pri izlaganju visokim kumulativnim dozama hidroklorotiazida, uz zaključak da korist od primjene hidroklorotiazida nadilazi moguće rizike<sup>2</sup>. Preporuka je HALMED-a da bolesnici trebaju nastaviti s primjenom propisane terapije i da samoinicijativno prekidanje liječenja može ozbiljno naštetiti pacijentima. Savjetuje se da pacijenti trebaju redovito provjeravati kožu zbog mogućeg nastanka bilo kakvih novih lezija ili promjena postojećih. Isto tako bolesnici bi trebali ograničiti izlaganje Sunčevoj svjetlosti i UV zračenju. HALMED navodi popis lijekova koji sadržavaju hidroklorotiazid koji se nalaze u prometu u Republici Hrvatskoj<sup>2</sup>, što je prikazano u **tablici 1**.

Ova su upozorenja objavljena nakon publiciranih rezultata dobivenih analizom podatka Danskoga registra<sup>3,4</sup>. No, već je prije bilo radova koji su izvijestili o mogućoj povezanosti tiazidskih diuretika i rizika za nastanak karcinoma kože i usnica<sup>5-7</sup>. Ono što je pobudilo dodatnu pozornost u danskim rezultatima jest potvrda o važnosti kumulativne doze, tj. rizik je to veći što je kumulativna doza veća. Na razmišljanje i oprez potiče podatak da se, uz dozu hidroklorotiazida od 12,5 mg na dan, što je najčešće primjenjivana doza u našim prostorima, kumulativna doza nakon pet godina uzimanja penje na 22.812 mg uz što je rizik za nastanak karcinoma usnice OR 3,9 (3,0 – 4,9), a rizik za nastanak karcinoma kože nakon deset godina je OR 1,29 (1,23 – 1,35) za bazocelularni i 3,98 (3,68 – 4,31) za planocelularni karcinom kože<sup>3,4</sup>. Slični podatci, ali s nižim stupnjem značajnosti dobiveni su i u *Kaiser Permanente Northern California US* kohorti<sup>8</sup>.

Premda istraživanja imaju svoju snagu, ona imaju i ograničenja. Činjenica da je opažen povećan rizik za pojavu navedenih karcinoma uz kumulativne doze hidroklorotiazida ne može se i ne smije ignorirati. No, isto tako treba biti svjestan činjenice da je korist od primjene tiazidskih diuretika nekoliko puta veća od rizika za nastanak karcinoma, što je posebice očito u starijih osoba, u bolesnika sa srčanim zatajavanjem i u onih s očekivanim kraćim trajanjem života<sup>9</sup>.

Nije zanemariv podatak da se takvi karcinomi mogu rano i na vrijeme dijagnosticirati ako su bolesnici pravilno informirani o provjeravanju promjena na koži i usnicama.

rothiazide treatment should be reconsidered in patients who were previously treated for non-melanoma skin cancer.

The Agency for Medical Products and Medical Devices of Croatia (HALMED; *Hrvatska agencija za lijekove i medicinske proizvode*) has published a statement on November 22, 2018 in which they warn of the slightly increased risk of non-melanoma skin cancer due to exposure to high cumulative doses of hydrochlorothiazide, with the conclusion that the benefits of hydrochlorothiazide application outweigh the potential risks<sup>2</sup>. HALMED's recommendation is for patients to continue with the application of the prescribed treatment and that self-induced treatment termination can cause serious harm to patients. The advice is for patients to regularly check their skin for possible manifestations of any new lesions or changes in existing ones. It is also recommended that patients limit exposure to sunlight and UV radiation. HALMED provided a list of medications containing hydrochlorothiazide that are on the market in the Republic of Croatia<sup>2</sup>, as shown in **Table 1**.

This warning is a result of the publication of the results obtained from data analysis performed on a Danish registry<sup>3,4</sup>. However, there had been earlier papers reporting the possible association between thiazide diuretics and risk of skin and lip carcinoma<sup>5-7</sup>. What caused special attention in the Danish results was confirmation of the importance of cumulative doses, i.e. that the risk is greater for higher cumulative doses. A cause for concern and caution is also the fact that with a dose of 12.5 mg daily, which is the most commonly applied dose in our region, the cumulative dose after five years of treatment is equal to 22.812 mg, with an OR for risk of lip carcinoma of 3.9 (3.0-4.9) and the risk of skin cancer after ten years at OR 1.29 (1.23-1.35) for basal-cell carcinoma and OR 3.98 (3.68-4.31) for squamous cell carcinoma<sup>3,4</sup>. Similar data, but with a lower level of significance, were also obtained in the *Kaiser Permanente Northern California US* cohort<sup>8</sup>.

Although these studies have certain strengths, they have limitations as well. The fact that increased risk of these carcinomas with cumulative doses of hydrochlorothiazide has been observed cannot and must not be ignored. However, we must also be aware of the fact that the benefits of the application of thiazide diuretics is several times greater than the risk of carcinoma, which is especially evident in elderly persons, patients with heart failure, and those with a shorter life expectancy<sup>9</sup>.

It is also important to note that these carcinomas can be diagnosed early and in a timely manner if the patients are properly informed on how to monitor changes on the skin and lips.

**TABLE 1. List of medications containing hydrochlorothiazide that are on the market in the Republic of Croatia<sup>2</sup>.**

Amicor H	Enap-H	Laaven-HL	Monopril plus	Prinzide	Valnorm H
Ampril HD	Enap-HL	Lizinopril H Farmal	Nebilet plus	Ramicomp Genericon	Valsacombi
Ampril HL	Exforge HCT	Lodoz	Olmesartan/hidroklorotiazid Genericon	Ramipril H Farmal	Vitozid
Blocar Plus	Fortzaar	Lorista H	Optimon Plus	Ramzid	Zofecard Plus
Cilazil Plus	Hyzaar	Lorista HD	Osan Plus	Skopryl plus	
CoAprovel	Iruzid	Losartic Plus	Piramil H	Tolucombi	
Co-Cazaprol	Kandapres Plus	Lotan H	Piramil HL	Tritazide	
Co-Diovan	Laaven-HD	MicardisPlus	Prilen Plus	Val plus	

## Zaključci

1. Rizik od nemelanomskoga karcinoma kože i usnica veći je u bolesnika liječenih hidroklorotiazidom nego što je u osoba koje nisu liječene ovim lijekom. Rizik se povećava s dužinom trajanja liječenja, tj. s kumulativnom dozom.
2. Mehanizam karcinogenosti hidroklorotiazida temelji se na fotosenzitivnosti. UV zračenje dovodi do disocijacije kloridnoga dijela molekule lijeka, čime se stvara pretpostavka za sintezu slobodnih radikala kisika i posljedično oštećenje molekule DNK.
3. Korist od primjene hidroklorotiazida veća je od rizika.
4. Omjer koristi i rizika napose je veći u starijih i teže bolesnih osoba.
5. Bolesnik mora biti informiran o postojećem riziku.
6. Bolesnik mora biti informiran o postojećoj alternativnoj terapiji koja je na raspolaganju u Hrvatskoj.
7. Svaki liječnik mora u svakoga pojedinog bolesnika procijeniti omjer koristi i rizika te nakon razgovora s bolesnikom odlučiti nastavlja li terapiju hidroklorotiazidom ili se odlučuje za postojeću alternativu.
8. Svim bolesnicima, a napose bolesnicima koji su liječeni hidroklorotiazidom, treba preporučiti uporabu adekvatne fotoprotekcije i redovito provjeravanja pojave ili promjena na koži.

## Conclusions

1. The risk of non-melanoma cancer of the skin and lips is higher in patients treated with hydrochlorothiazide than in persons not treated with this medication. The risk increases with treatment duration, i.e. with cumulative doses.
2. The carcinogenic mechanism of hydrochlorothiazide is based on photosensitivity. UV radiation leads to the dissociation of the chloride part of the drug molecule, allowing the synthesis of oxygen free radicals and consequent damage to the DNA molecule.
3. The benefits of hydrochlorothiazide application outweigh the risks.
4. The risk-benefit ratio is increased in elderly and severely ill persons.
5. Patients must be informed of the existing risk.
6. Patients must be informed of existing alternative therapy that is available in Croatia.
7. Every physician must make an individual risk-benefit ratio assessment for every patient and, after conferring with the patient, decide whether to continue hydrochlorothiazide treatment or opt for an available alternative.
8. The use of adequate photoprotection and regular examinations for appearances and skin changes should be recommended to all patients, especially those receiving hydrochlorothiazide treatment.

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