Prevalence of hepatitis C virus infection in adults with the risk factors

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ABSTRACT

In 2017 chronic hepatitis C (CHC) seems to be a curable disease in most cases. Analysis of epidemiologic data of hepatitis C virus (HCV) infection gained from a primary care office shows how HCV is underdiagnosed in the Czech Republic (CZ). The importance of primary care in screening of HCV infection is shown, as is the necessity of spreading information about this disease between common population and healthcare workers. The aim of the study is to determine seroprevalence of HCV antibodies and HCV ribonucleic acid (RNA) positivity among registered patients with risk factors (RF) in medical history in one physician´s practice. 1620 complete follow-ups of registered clients were accomplished during a 10-month period between 2016 and 2017 in the office of one general practitioner (GP). Amongst those 627 were confirmed to have RF. Each client with RF was tested for HCV antibodies, including detection of HCV RNA via polymerase chain reaction (PCR) method in cases of HCV antibodies positivity. 19 anti HCV positive clients were found, with a prevalence of 3.03%, 5 were HCV RNA positive, with a prevalence of 0.8%.

KEY WORDS

HCV infection – underdiagnosed – screening – primary care

SOUHRN

Dyrhonová M., Hašková K., Vránová J., Chlíbek R.: Prevalence infekce virem hepatitidy C u dospělých s rizikovými faktory

Chronickou hepatitidu C (CHC) lze v současné době již pokládat za vyléčitelné onemocnění v naprosté většině případů. Analýza epidemiologických dat o infekci virem hepatitidy C (HCV) získaných v ambulanci praktického lékaře (PL) poukazuje na podhodnocení této diagnózy v České republice. Ukazuje na důležitost primární péče ve vyhledávání HCV infekce v populaci i na potřebu šíření poznatků o této nemoci mezi laiky i zdravotníky. Cílem této práce je stanovení prevalence anti HCV protilátek a přítomnosti ribonukleové kyseliny (RNA) HCV u jedinců s rizikovou anamnézou v ambulanci PL. Během 10 měsíců v roce 2016-2017 bylo v jedné ambulanci PL provedeno 1620 komplexních vyšetření registrovaných klientů. Z těchto vyšetřených bylo 627 určeno jako rizikových. Každý rizikový jedinec měl proveden test na detekci anti HCV protilátek, včetně detekce HCV RNA metodou polymerázové řetězové reakce (PCR) v případě anti HCV pozitivity. Anti HCV pozitivních bylo celkem 19, prevalence 3,03 %, z nich 5 mělo detekovanou HCV RNA, prevalence 0,8 %.

KEYWORDS

HCV infekce – podhodnocení – vyhledávání – primární péče – séroprevalence

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INTRODUCTION

HCV can have an acute or chronic course of disease. Acute hepatitis is most commonly asymptomatic and is seldomly diagnosed. Chronic hepatitis can be symptom free for years, but the long-term inflammatory necrotic processes in the parenchyma of the liver lead to significant increase in morbidity and mortality with increased risk of liver cirrhosis (CIH), hepatocellular carcinoma (HCC), risk of hepatic failure and extrahepatic manifestations [1–4]. Disease, which remains unnoticed for years, is often diagnosed when symptoms first appear, this often signalizes significant damage to the liver with all consequences and complications that are responsible for 500 000 deaths yearly worldwide [5]. The global prevalence of hepatitis C (HC) is 3%. 180–200 million individuals infected with HCV are reported in total [6]. In Europe there are 9 million individuals with CHC, the prevalence is 0.5–3.5%, with the highest occurrence in the Mediterranean [7, 8]. Genotype (GT) 1 is most common in Europe and the USA, however the number of people infected with GT 3 is rising rapidly in Europe, including CZ [9–17]. The prevalence in CZ is 0.6% of the population, which is at least 60 000 patients [18]. Currently, the number of newly reported cases of HCV infected people is around 750–950 people annually [19]. A seroprevalence overview was conducted in CZ in 2001 and the prevalence of antibodies was 0.2% [20]. After this no other larger overview has been conducted for 14 years, but it is assumed that the prevalence is on the rise. Only in 2015 3000 adult subjects from three centres (Hradec Králové, Brno, České Budějovice) were tested and in this group the prevalence was 1.67% for anti HCV antibodies and 0.93% for HCV RNA positive sera, with the largest number in the group of 30-34-year-olds [21]. There is no population screening in CZ which would be similar to the testing of 'baby boomers' in the USA, for example [22]. Only a small amount of people infected with HCV are revealed. The estimate is that around 20-50% of the diseased individuals are not diagnosed, therefore, are not treated. The prevalent problem is insufficient awareness and knowledge of the lay and professional public and insufficient search methods of infected individuals. Only screening of blood donors who are registered in blood

transfusion departments, which was launched in 1992 in CZ with the testing of specific antibodies against HCV using ELISA (enzyme-linked immunosorbent assay), and later CMIA (chemiluminescent microparticle immunoassay) and ECLIA (electrochemiluminescent immunoassay) to the increase of quality of *in vitro* diagnostics. There is no standard in primary care that would allow blanket testing of infected individuals in CZ. Mathematical models predict a decrease in the number of infected with HCV by 2030, also with the ageing of the population an increase in the number of those with higher degrees of liver fibrosis (LF), CIH, HCC and those who will undergo transplant is predicted [23]. In a country with no screening of the population, without a surveillance database, seroprevalence overviews of the adult population are the gold standard for figuring out prevalence of anti HCV antibodies [24].

The main objective of the study was to find out the prevalence of HCV antibodies in the office of a GP amongst adult clients who were identified of risk for HCV infection. The secondary objective was to identify the most relevant RF in this group of investigated people and to find the dominant genotype of infected individuals with CHC.

MATERIALS AND METHODS

Study design, choice of subjects

This study was led as monocentric in a country district in the Central Bohemian region in one of the offices of a GP as a seroprevalence analysis. From October 2016 until August 2017, 1620 adult (over 18 years-old) clients registered with GP were completely examined with an accent on epidemiologic history, physical examination and liver test results, levels of albumin and thrombocyte count. Because analyses were provided during regular visit as a part of medical care for patients, no written consent or ethics committee approval were required. Individuals with history involving RF were selected, meaning those, who belonged to one of the predefined groups. From an epidemiological point of view 12 groups were formed of individuals with RF that may lead to higher probability of acquiring HCV infection:

1. Recipients of blood derivates, blood transfusions (TRF), surgeries, trauma or abortions before 1992
2. Liver tests (LT) levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) elevated above normal
3. Individuals with history of injectable recreational drug application
4. Individuals with history of haemodialysis (acute and regular)
5. Sexual partners of HCV positive individuals
6. Medical personnel
7. Individuals with tattoos and/or piercing
8. Individuals with prior imprisonment
9. Recipients of organ transplants
10. Children of HCV positive mothers
11. Haemophiliacs treated before 1987
12. Individuals infected with Human Immunodeficiency Virus (HIV)

Also, individuals with deficient albumin levels or thrombocyte count, or pathologies in physical findings were included in the study. Part of the physical examination was determination of jaundice, spider naevi, unnormal size and consistency of the liver, enlargement of the spleen, oedema of the lower extremities, signs of tattoos. 627 of the examined individuals were identified as of risk. Those 627 people gave venous blood to determine presence of HCV antibodies.

Testing for anti HCV antibodies

All 627 individuals had their serum tested in qualitative detection of anti HCV antibodies using ECLIA, Anti-HCV II kit from Roche was used (for use inside the immunochemical analyser Cobas e 601, Roche). The results were in form of cut-off indexes (sample signal/cut-off), samples with cut-off indexes < 0.9 were identifies as non-reactive, samples with cut-off indexes from 0.9 to < 1.0 were identified as borderline, and samples with cut--off indexes ≥ 1.0 were identified as reactive. Individuals with reactive samples were tested positive.

HCV detection, genotyping

In samples with borderline or reactive results, we proceeded with laboratory testing of the blood samples for HCV RNA detection via Cobas®HCV test, Roche with the use of Cobas®4800 system, Roche (isolation and detection). HCV genotyping: amplification – VERSANT® HCV Amplification 2.0 (LiPA), Roche, primers for 5'UTR (5'untranslated region) and core region; detection-VERSANT® HCV Genotype 2.0 (LiPA), Roche, reverse hybridization method (product created by reverse transcription polymerase chain reaction (RT-PCR) amplification of the mentioned area is hybridized on oligonucleotide probes, which are connected to a nitrocellulose strip). GT HCV was identified in HCV RNA positive samples. Parameters: sample type-serum, EDTA plasma (plasma with Ethylene diaminetetraacetic salt), sample volume – 400 µl or 200 µl (so-called paediatric volume), analytical sensitivity – 9.2 IU/ml (400 µl), 15.3 IU/ml (200 µl), linear range 400 µl: 15.0–1.0 x 10^8 IU/ml, 200 µl: 25.0–1.0 x 10^8 IU/ml, detected HCV genotypes 1–6.

Statistical analysis

Patients were divided into groups according to the following criteria: age (< 40 years-old vs. ≥ 40 years-old), sex, recreational drug use (yes vs. no), HCV detection (negative vs. reactive). The descriptive statistic method was used for presentation of results: calculation of absolute and relative frequency tabs, also calculation of basic parameters of the group of patients – averages, deviations, medians, ranges of monitored variables. For statistical analysis STATISTICA 9.0 programme (StatSoft Inc.) was used.

RESULTS

Characteristics of investigated risk population

From 2016 to 2017 1620 patients were tested in a regular office of a GP for adults. 627 in total were identified to have at least one of the defined RF for acquiring HCV infection. The average age of all 627 subjects was 46.1 years-old, the median age was 45 (19-82 years-old). There were 245 people in the age group under 40 and 382 in the ≥ 40 group. In this group there were 283 men and 344 women. Except for children of HCV positive mothers, haemophiliacs treated before 1987 and people infected with HIV all the other defined groups of people with RF

were present in this cohort. The largest group was of those who have received medical care (groups 1 and 4 – recipients of blood derivates, TRF, surgery, trauma, and abortions before 1992, haemodialysis) 388 people, prevalence of 24%, the next largest group were individuals with alternated liver tests with a total of 176, prevalence of 10.9% and the group of medical personnel which counted 102 people, with a prevalence of 6.3%. Individuals with tattoos and/or piercing counted 43, with a prevalence of 2.7%. From the entire group of 1620 people, there were 7 individuals who admitted prior recreational drug use, with a prevalence of 0.43%, 5 people were imprisoned in the past, with a prevalence of 0.31%, 3 people admitted to having sexual contact with HCV positive individuals, prevalence of 0.2% and 3 (0.2%) have received organ transplants (1 heart transplant, 2 kidney transplants).

Prevalence of anti HCV positivity
From 627 tested sera 19 samples were positive (9 males, 10 females), prevalence of 3.03%. 7 tested positive in the age group < 40 and 12 in the ≥ 40 age group. 4 of the positive individuals admitted to experimenting with recreational drugs, 11 received medical care, 3 were imprisoned in the past and one was the partner of an HCV infected woman. Only 12 patients out of 19 who tested HCV positive had elevated transaminases (ALT or/and AST) and only 4 (out of 19) knew about their HCV infection and were followed by a specialist. For everyone else the information about their HCV status was new and surprising.

Prevalence of HCV RNA positivity
Amongst the 19 individuals with positive specific anti HCV antibodies 5 were HCV RNA positive with CHC, prevalence of 0.8%. The average age of patients with CHC was 58.4 years (ranging from 39 to 80 years), 4 males, prevalence of 0.64% and 1 woman 0.2 %, only one person was under 40 years old, the other 4 were older.

Genotype of HCV
Amongst the HCV RNA positive individuals all 5 with viremia had GT 1b, other genotypes were not found in our cohort.

Determination of level of LF in patients with CHC
All 5 HCV RNA positive individuals had CHC. An essential part of the examination of this type of patients is determining the clinical stages of LF. When staging LF, different criteria and scoring systems may be used. To maximally simplify these systems METAVIR scoring system was introduced into practice and is now widely used [25]. This system divides the stages of fibrosis into 5 stages METAVIR F0–F4. Stage F0–F1 means findings without fibrosis, F2 means significant fibrosis, F3 bridging fibrosis and F4 means liver cirrhosis. Currently, the preferred method for detecting the stage of LF is with non-invasive detection. In the case of our patients the degree of LF was tested with shear wave elastography, a method the uses shear waves. These waves appear as a response of the elastic resistance of tissue to mechanical vibration with low frequency (10–500 Hz) and spread through the entire tissue volume in transverse direction. Shear waves can only spread through environment which resists shear stress, this happens only solid environment. Elasticity of tissue, the so-called Young module, can be estimated based on measuring the speed of spread of shear waves in tissue. We usually enforce the density of biological tissues as a constant. The average liver density is approximately 1047 ± 5 kg/m3, elasticity is measured in kilopascals (kPa) [26]. Liver elasticity of our patients was METAVIR F2 in 2 cases. There are F3 in 2 cases and F4 in 1 case, in which HCC was also diagnosed. With exception of the man with CIH (F4) patients did not have any subjective complaints. Even in the case of this man the main complaints reflected the symptoms of a growing HCC with generalisation, anorexia, pain in the right hypochondrium, growing malnourishment and finally death.

DISCUSSION

This study was conducted in a cohort of adult patient population in a regular office of a GP in CZ in the time of repossession of clientele by the new physician from the former one. The new physician was acquainted with his patients gradually, completely randomly as they entered the office with their acute problems and wishes. During this first contact everyone's available medical documentation was processed, complete medical history was supplemented, a physical examination was conducted. Judging by all this information, those who had pathological liver test values, lower platelet counts and/or lower albumin values in at least one of the prior three laboratory finding, and those who currently had pathologic finding during physical examination, which supported suspicion of liver damage were chosen, also those who had identified RF listed above in their medical history.
In our cohort we obtained data, which shows being treated in a healthcare facility as the highest RF. Among anti HCV positive there were 11 out of 19 individuals. Contrary to this, amongst the large amount of tested healthcare personnel (102 out of the total number of 1620, prevalence of 6.3%) none were confirmed to have HCV infection, which shows us the low risk of HCV spread from the infected individuals onto medical personnel when all safety percussions are taken, also this shows the low total prevalence of people infected with HCV in the population. In this study a large group of people (2.7%) who had had tattoos and/or piercing were tested. We did not find anyone with HC in this group. There is no comprehensive data on the number of individuals with experience with intravenous recreational drug applications, their numbers are estimated to be from 0.4% to 3% [27]. In its annual report on the status in drug matters in 2013 in CZ the National monitoring centre for drugs and addiction estimated about 44.9 thousand problem drug users. Buprenorphine is on the rise. The phenomena of the last years is the emergence of new synthetic drugs from the cathinone or the phenethylamine group – experience with these drugs plays a major part in the problem of drug usage – about one third in Prague, but only a small fraction reports it as their primary drug [28]. Numbers of individual who have joined the substitution programme for addiction on opiates/opioids in CZ is also known. 529 cases of treatment in 446 people were added to the register in 2017 [29]. In our cohort 7 people admitted experimenting with recreational drugs, prevalence of 0.43%.

Incidence of new cases of HC in CZ was highest in 1999, from then on it has a declining tendency and has been relatively stable in the last few years. According to mathematical models a further decline is anticipated. On the other hand, increase in patient of middle and older age with higher degrees of fibrosis, compensated and decompensated CIH, CHC and related deaths are predicted [30]. In our cohort seroprevalence of anti HCV antibodies and HCV RNA positivity is found mostly in individuals who are 40-years-old and older, also higher stages of fibrosis are found in this age group, which correlates with mathematical models mentioned above. GT 1, which is most common in the world, is prevalent mainly in developed countries with high income. Its spread is connected mainly to administered transfusions of blood derivates before HCV was discovered in 1989 [28]. GT 3a, on the other hand, the second most common globally, mainly in Europe is associated with intravenous recreational drug abuse [31, 32, 33] and also with migration to Europe from high incidence countries (India, Pakistan) [34]. This data is consistent with our results, only GT 1b was detected. Those were people, who reported any of the possible means of transmission of HCV, while receiving medical treatment in a healthcare facility – applied blood derivates, TRF, surgeries, injuries and abortions prior to 1992, those who had haemodialysis or received organ transplants.

In comparison the results of a study from 2001 (0.2%) and from 2015 (1.67%), even with the knowledge, that we targeted people with RF in their personal history, we can confirm that prevalence of anti HCV antibodies and prevalence of CHC in the adult population in CZ has increased in the last 16 years. Unlike the study conducted in 2015 we found more anti HCV positive individuals and more people with CHC in the age group of 40 years and older.

Aside from the study, on closer examination, the main reason of elevated ALT and AST was steatohepatitis due to metabolic syndrome, non-alcoholic steatohepatitis (NASH) with obesity, dyslipidaemia and diabetes mellitus.

CHC is not solely a disease of the liver with extrahepatic complications, it carries with it a change in quality of life, the stigma of disease, it has a psychosocial dimension, it decreases work productivity and has a noticeable economic impact.

We share our results that show a need for a targeted search of people with HC. In CZ there is an increase in people with CIH, who will need liver transplant because of decompensated disease or development of HCC is anticipated. For reduction of morbidity and mortality as a result of CHC a more effective screening than the one used now in CZ is needed, together with an increase of availability of treatment with direct acting antiviral drugs (DAA), which are highly effective, with minimal side-effects. They have a potential to cure all the infected people and, in the future, will lead to eradication of HC. The only crucial obstacle to the spread of this treatment is high price.

There are studies in the world that compare the economic impact of targeted or whole population screening of anti HCV antibodies and antiviral treatment in comparison to treatment of compensated a decompensated CIH. One of the last analyses conducted in South Korea shows the cost-effectiveness of testing was highest when performed in subjects under 40 year of age [35]. The conclusion of a study performed in 2013 in the USA, targeted screening is cost-effective, if the prevalence of HCV is above 0.84% [36]. The strategies of search of patient with HC in CZ should be reconsidered due to all the available epidemiologic data, which we do not have enough of, expanding and refinement is needed.

CONCLUSIONS

In comparison to the data available from 2001, and from 2015 an increase of seroprevalence of anti HCV positivity in the adult population is noted. In our cohort of adults with defined of acquiring HCV infection (anti HCV prevalence of 3.03%) the dominant group was patients with documented surgeries or trauma, those who have received blood transfusion or blood derivates prior to 1992 and dialyzed patients (24%). On the other hand, the group with history of intravenous drug use were in the minority (0.43%), this, however, corresponds with the estimated number of occurrences in CZ. Patients with CHC (prevalence of 0.8%) are diagnosed at a higher age (average of 58.4 years-old) and with a higher degree of LF (≥ F2), there are more males than females (4:1). Only GT 1b was detected, which corresponds with the high representation of those who were exposed to medical interventions in healthcare facilities, whereas GT 3a, which is associated with drug abuse, was not detected. Since the epidemiological situation in CZ has a slower change of trends compared to Western Europe and North America, we can predict an increase of GT3 in the future [21].

Our results show the need for a systemic search for patients with HC, more so in the high-risk adult population, we need a change for a more effective screening method in CZ. The general awareness of laymen and experts is insufficient. This is all followed with insufficient reporting of diagnosis, growing morbidity and mortality as a result of complication of CHC and the cost for the entire population which this brings.

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LÉČBA CHRONICKÉ HEPATITIDY C

KOMBINACE 2 DAA* V 8TÝDENNÍM PANGENOTYPOVÉM REŽIMU[1]

=8 TÝDENNÍ LÉČBA

DOSUD NELÉČENÍ PACIENTI BEZ CIRHÓZY, PACIENTI S INFEKCÍ GT1–6[1†]

98 %[2]
ITT‡
VYLÉČENÝCH PACIENTŮ** (SVR12)

Napříč GT 1–6 (n = 943/965)[2]
*DAA = přímo působící antivirotika.
**Vyléčení = setrvalá virologická odpověď (SVR12) definovaná jako HCV RNA nižší než LLOQ za 12 týdnů po ukončení léčby a byla primárním účinnostním cílovým ukazatelem ve všech studiích.
†8týdenní léčba je také doporučena u pacientů bez cirhózy dříve léčených pomocí pegIFN + RBV s nebo bez SOF nebo SOF + RBV s HCV infekcí genotypu 1, 2, 4, 5 a 6.
‡ITT = do analýzy jsou zahrnuti všichni pacienti, kteří byli zařazeni do studie.

Zkrácené informace o léčivém přípravku Maviret 100 mg/40 mg potahované tablety
Složení: Jedna potahovaná tableta obsahuje glecaprevirum 100 mg a pibrentasvirum 40 mg. **Indikace:** Léčba chronické virové hepatitidy C u dospělých. **Dávkování a doba léčby:** Doporučená perorální dávka přípravku Maviret je 300 mg/120 mg (tři tablety 100 mg/40 mg) jednou denně s jídlem. Doporučená doba trvání léčby viz SPC. ***Zvláštní populace:*** U pacientů s poruchou funkce ledvin a lehkou poruchou funkce jater není třeba dávku upravovat; u pacientů se středně těžkou poruchou funkce jater se Maviret nedoporučuje, těžká porucha funkce jater – viz kontraindikace. U pacientů po transplantaci jater nebo ledvin s cirhózou nebo bez ní je doporučena doba léčby 12 týdnů. Další informace týkající se dávkování viz SPC. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. Pacienti s těžkou poruchou funkce jater (Child-Pugh C). Současné použití s léčivými přípravky obsahujícími atazanavir, atorvastatinem, simvastatinem, dabigatran-etexilátem, přípravky obsahujícími ethinylestradiol, silnými induktory P-gp a CYP3A (např. rifampicinem, karbamazepinem, třezalkou tečkovanou (Hypericum perforatum), fenobarbitalem, fenytoinem a primidonem). **Těhotenství a kojení:** Údaje o podávání glekapreviru nebo pibrentasviru těhotným ženám jsou omezené nebo nejsou k dispozici. Přípravek Maviret není z preventivních důvodů během těhotenství doporučován. **Zvláštní upozornění:** Reaktivace viru hepatitidy typu B: Pacienti s koinfekcí HBV/HCV jsou vystaveni riziku reaktivace HBV, a proto mají být monitorováni a má jim být poskytnuta péče podle aktuálních standardních léčebných postupů. Screening HBV má být u každého pacienta proveden ještě před zahájením léčby. Porucha funkce jater: Maviret se nedoporučuje u pacientů se středně těžkou poruchou funkce jater (Child-Pugh B) a je kontraindikován u pacientů s těžkou poruchou funkce jater (Child-Pugh C). Pacienti, u kterých selhal předchozí režim zahrnující inhibitor NS5A a/nebo inhibitor NS3/4A: Přípravek Maviret není doporučen pro opakovanou léčbu pacientů s předchozí expozicí NS3/4A a/nebo NS5A. Laktosa: Přípravek Maviret obsahuje laktosu. Pacienti se vzácnými dědičnými problémy s intolerancí galaktosy, vrozeným deficitem laktázy nebo malabsorpcí glukosy a galaktosy nemají tento přípravek užívat. U diabetiků může po zahájení léčby infekce HCV přímo působícími antivirotiky dojít ke zlepšení kontroly glykemie, což může potenciálně vést k symptomatické hypoglykemii. U diabetiků, u nichž je zahájena léčba přímo působícími antivirotiky, je třeba pečlivě monitorovat glykemii, zejména v prvních 3 měsících, a v případě potřeby upravit jejich antidiabetickou medikaci. O zahájení léčby přímo působícími antivirotiky je třeba informovat lékaře, který má u pacienta na starosti léčbu diabetu.* **Interakce:** Glekaprevir a pibrentasvir jsou inhibitory P-glykoproteinu (P-gp), proteinu rezistence karcinomu prsu (BCRP) a polypeptidu transportujícího organické anionty (OATP) 1B1/3. Současné podávání přípravku Maviret s léčivými přípravky, které jsou substráty P-gp BCRP nebo OATP1B1/3 může zvýšit jejich plazmatickou koncentraci a může vyžadovat úpravu jejich dávky. Současné podávání přípravku Maviret s léčivými přípravky, které jsou středně silnými induktory P-gp/CYP3A (např. oxkarbazepin, eslikarbazepin, lumakaftor, krizotinib), může snížit plazmatické koncentrace glekapreviru a pibrentasviru a není tedy doporučeno. Současné podávání přípravku Maviret s léčivými přípravky, které inhibují P-gp a BCRP (např. cyklosporin, kobicistat, dronedaron, itrakonazol, ketokonazol, ritonavir), může zpomalit eliminaci glekapreviru a pibrentasviru a tím zvýšit plazmatickou expozici antivirotik. Léčivé přípravky, které inhibují OATP1B1/3 (např. elvitegravir, cyklosporin, darunavir, lopinavir), zvyšují systémové koncentrace glekapreviru. Pacienti léčení antagonisty vitaminu K: Během léčby přípravkem Maviret se může změnit funkce jater, je doporučeno pečlivé monitorování hodnot INR. **Nežádoucí účinky:** Velmi časté: bolest hlavy a únava. Časté: průjem, nauzea, astenie. Zvýšení celkového bilirubinu nejméně na 2násobek horní hranice normálních hodnot (ULN) bylo pozorováno u 1,3 % pacientů v souvislosti s inhibicí transportérů bilirubinu zprostředkovanou glekaprevirem a jeho metabolismem. **Uchovávání:** Žádné zvláštní podmínky uchovávání. **Balení:** PVC/PE/PCTFE blistr s Al fólií, balení obsahuje 84 (4x21) tablet. **Držitel rozhodnutí o registraci:** AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Německo. **Registrační číslo:** EU/1/17/1213/001. **Poslední revize textu:** 11/2018. Přípravek je vázán na lékařský předpis a je hrazen z prostředků veřejného zdravotního pojištění. ▼ **Tento léčivý přípravek podléhá dalšímu sledování. To umožní rychlé získání nových informací o bezpečnosti. Žádáme zdravotnické pracovníky, aby hlásili jakákoli podezření na nežádoucí účinky.** *Seznamte se, prosím, s úplnou informací o přípravku dříve, než jej předepíšete.* * Všimněte si, prosím, změn v informacích o léčivém přípravku.

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