Diseases with hepatitis C virus (HCV) aetiology are rarely diagnosed on the basis of the clinical picture because they are usually asymptomatic or only mildly symptomatic for many years. Consequently, diagnosis is often preceded by incidental detection of laboratory markers indicative of HCV infection. Studies conducted in Poland in recent years have demonstrated that anti-HCV antibodies are found in 0.9-1.9% of Poland’s inhabitants, depending on the study population and methodology. The studies have indisputably confirmed the presence of HCV RNA in the blood, indicating active infection, at 0.6%. This figure is equivalent to approximately 200,000 adult members of the Polish population who require urgent diagnosis and treatment. The estimated number of patients diagnosed during the period of availability of HCV therapy is approximately 30,000, which corresponds to a detection rate of 15% [1-3].

Around 20-40% of acute infections are believed to resolve spontaneously. Hepatitis C virus infection only becomes apparent after many years. One in five chronic infection cases are diagnosed at the stage of advanced pathological changes in the liver, i.e. cirrhosis or, less commonly, hepatocellular carcinoma. Hepatitis C virus infection also triggers a range of extrahepatic syndromes – usually cryoglobulinaemia, which produces clinical manifestations in 5-25% of cases [4].

Treatment should be provided to all HCV-infected patients diagnosed with acute and chronic hepatitis and the fibrosis stage F ≥ 1. The primary aim of therapy is to halt or reverse histological lesions, particularly liver fibrosis [5-7].

Treatment should preferably be initiated at early stages of the disease due to higher efficacy. However, in the event of problems with the availability of drugs, priority should be given to the following sub-groups of patients:

- with liver fibrosis (F ≥ 3),
- waiting for liver transplantation or who have had liver transplantation,
- undergoing haemodialysis, especially patients waiting for kidney transplantation,
- with extrahepatic manifestations of HCV infection (membranous glomerulonephritis, cryoglobulinaemia, lichen planus, cutaneous porphyria, B-NHL lymphomas and others),
- with hepatocellular carcinoma with HCV aetiology,
- co-infected with hepatitis B virus (HBV).

Acute HCV infection

The sole objective criterion in the diagnosis of acute hepatitis C (AHC) is the presence of laboratory markers indicative of AHC (elevated alanine aminotransferase activity, anti-HCV and/or HCV RNA) in patients whose prior HCV tests were negative or with patients after documented exposure to HCV infection. In other cases, the diagnosis of acute hepatitis C may be inconclusive. It is important to note that while HCV RNA is detectable as early as 1-3 weeks after infection, anti-HCV antibodies cannot be detected until 4-10 weeks after HCV infection. After the onset of the first clinical symptoms, if they occur, anti-HCV antibodies are present only in 50-70% of infected individuals, and it takes three months for the figure to reach 90%. What is more, some patients do not develop anti-HCV antibodies at all. In such cases, HCV infection is diagnosed by determining the presence of HCV RNA.

Therapy can be considered if HCV RNA is still detectable at week 12 after the onset of the first clinical symptoms or determination of laboratory markers. Treatment should be based on pegylated interferon α
(PegIFNα) 2a or 2b administered in monotherapy for 24 weeks. In cases of HIV-HCV co-infection, combined therapy with ribavirin (RBV) should be considered [6].

### Chronic HCV Infections

The diagnostic criterion for chronic diseases with HCV aetiology is the presence of HCV RNA (in blood serum, liver tissue or peripheral blood mononuclear cells) sustained for at least six months in a patient with markers of liver disease or an extrahepatic manifestation of infection. Chronic HCV infections may take the form of chronic hepatitis C and cirrhosis or hepatocellular carcinoma. The selection of treatment regimen should involve determination of the virus genotype and assessment of the stage of liver fibrosis. Therapy should be monitored by assaying the concentration of HCV RNA by techniques ensuring that the limit of detection is below 15 IU/ml for qualitative assessment, and does not exceed 25 IU/ml for quantitative assessment.

### Drugs Recommended in the Treatment of Chronic HCV Infection

The recommendations include exclusively drugs which have been registered in any country worldwide, and especially drugs approved by the EMA (European Medicines Agency) or FDA (Food and Drug Administrations), as these medications are likely to be available on the Polish market (Table 1).

Other DAA drugs are also acceptable, provided that they are approved by the EMA or FDA, according to their SPC.

| Drug category | Class | Drugs | Daily dosage |
|---------------|-------|-------|--------------|
| Direct acting antivirals (DAA) | NS3 inhibitors (proteases) | Asunaprevir (ASV) | 200 mg/day in 2 doses |
| | | Boceprevir (BOC) | 2,400 mg/day in 3 doses |
| | | Paritaprevir (PTV) | 150 mg/day in 1 dose* |
| | | Simeprevir (SMV) | 150 mg/day in 1 dose |
| | | Telaprevir (TVR) | 2,250 mg/day in 2 doses |
| | NS5B inhibitors (polymerases) | Dasabuvir (DSV) | 500 mg/day in 2 doses |
| | | Sofosbuvir (SOF) | 400 mg/day in 1 dose** |
| | NS5A inhibitors | Daclatasvir (DCV) | 60 mg/day in 1 dose |
| | | Ledipasvir (LDV) | 90 mg/day in 1 dose** |
| | | Ombitasvir (OBV) | 25 mg/day in 1 dose* |
| Interferons | Pegylated interferons α (PegIFNα) | PegIFNα2α | 180 µg/week |
| | | PegIFNα2β | 1.5 µg/kg/week |
| Others | Ribavirin (RBV) | 1,000 or 1,200 mg at body weight < 75 kg or > 75 kg |

*PTV and OBV are combined in one tablet with ritonavir (PTV/OBV/r)  
**SOF can be combined in one tablet with LDV (SOF/LDV)

The following therapeutic regimens are applied in clinical practice:
- PegIFNα + RBV,
- PegIFNα + RBV + DAA,
- DAA + RBV,
- DAA + DAA +/- DAA +/- RBV.

### General Recommendations

- The selection of a therapeutic regimen must take into consideration the current availability, efficacy and safety profile, and must be preceded by providing the patient with easily understood information about the duration of therapy, potential adverse reactions associated with each drug, the importance of complying with the prescribed treatment regimen and rules governing therapy continuation and interruption.
- If adverse reactions occurring during triple drug therapy with interferon make it necessary to modify the treatment, the first step is to reduce the doses of RBV and/or PegIFNα. If the measure proves ineffective, DAA should be discontinued.
- Direct acting antivirals monotherapy is unacceptable due to the risk of selection of resistant strains.
- IL28B genotyping is not required during the selection of patients for treatment options because it restricts the accessibility of therapy without providing any pharmacoeconomic benefits [6].
- Testing for HCV mutations prior to the initiation of treatment is justified only in patients who are infected with genotype 1a, which is rarely detected in Poland. If the Q80K mutation is identified on the
viral genome in these patients, therapeutic regimens containing SMV should not be used.

- Liver fibrosis is assessed on a 5-point scale from 0 to 4 based on liver elastography performed using a technique allowing quantitative measurement of liver tissue stiffness expressed in kPa (SWE or TE), or liver biopsy. If coexisting liver diseases with a different aetiology are suspected, and the result of a non-invasive examination is not in accord with the patient’s clinical condition or discrepancies between results of various non-invasive tests are identified, liver biopsy is recommended (unless there are contraindications to the procedure) in order to provide a conclusive result. In rare cases of contraindications to performing liver biopsy and elastography, patients should receive treatment recommended for fibrosis stage F4 without undergoing fibrosis assessment [6].

- Treatment with a regimen containing PegIFNα may be considered effective if no HCV RNA is detected in the blood at week 24 after completion of therapy, signifying a sustained virological response (SVR24). In interferon-free therapies, sustained virological response is assessed 12 weeks after completion of treatment (SVR12). However, until indisputable results of studies investigating long-term efficacy of DAA treatment (especially without interferon) are obtained, ALT and HCV RNA monitoring at weeks 48 and 96 after the end of therapy is advisable. The efficacy of treatment should be assessed by methods whose lower limit of detection is < 15 IU/ml.

- HCV-infected people, especially with coexisting cirrhosis, should be systemically monitored for the development of hepatocellular carcinoma (HCC). Ultrasound examination of the liver and, if necessary, additional determination of α-fetoprotein (AFP) should be performed at 24-week intervals also after the completion of effective therapy. Assessment of AFP concentration should not be used alone for early diagnosis of HCC. However, it may be useful in determining the prognosis of diagnosed cancer and in therapy monitoring. If a cancer lesion is suspected, four-phase CT examination with contrast or MRI with contrast is recommended. Contrast-enhanced ultrasound, however, is not recommended for the routine diagnosis of HCC [8-13].

- The therapy of HBV-HCV or HIV-HCV co-infection is the same as the treatment recommended for infection with the HCV virus alone. As with other co-morbidities, patients should be assessed for possible drug interactions.

- Infections with all HCV genotypes in children (past 3 years of age) should be routinely treated with dual drug therapy (PegIFNα and RBV).

- Patients who have failed prior treatment based on PegIFNα, regardless of the stage of liver fibrosis, should be retreated with an alternative regimen which is expected to show significantly higher efficacy.

- Patients approved for liver transplantation including those who have had the procedure should first receive a treatment regimen without interferon, in accordance with recommendations listed in Table 2.

- The precondition for protecting the transplanted liver from HCV infection is the suppression of viraemia to undetectable levels at least a month prior to the transplantation procedure, which justifies the initiation of therapy as early as possible after approval for liver transplantation. However, if the expected period until the procedure is so short that it does not guarantee effective suppression of the virus, anti-HCV treatment should not be initiated, and the patient should be closely monitored for the relapse of viraemia in order to introduce interferon-free therapy as promptly as possible.

- Patients with contraindications to interferon α treatment (Table 3) or interferon α intolerance (Table 4) should be routinely prescribed interferon-free treatment.

Specific recommendations

The basic criteria for differentiating the therapeutic approach include HCV genotype and stage of liver fibrosis.

Infections with HCV genotype 1

Treatment of patients with mild liver fibrosis (F1-F2)

Triple drug treatment based on PegIFNα + RBV and DAA can be considered in patients who have not been previously treated or have had a relapse after a conventional dual drug regimen. Non-responders or partial responders to prior therapy based on PegIFNα should be retreated with an interferon-free regimen regardless of the stage of liver fibrosis.

Therapy with boceprevir

Triple drug treatment with boceprevir (BOC) can be considered in patients who have not been previously treated or have had a relapse of infection after ineffect-
### Table 2. Therapeutic options in the treatment of infections with different HCV genotypes

| Genotype | Population | Drugs | Duration of therapy |
|----------|------------|-------|---------------------|
| **1**    | Fibrosis at F1-F2 | BOC + PegIFNα + RBV, DCV + ASV, PTV/r/ObV + DSV, PTV/r/ObV + DSV + RBV, SOF + DCV, SOF/LDV, TVR + PegIFNα + RBV, SMV + PegIFNα + RBV, SOF + PegIFNα + RBV | 28-48 weeks (incl. 24-32 weeks of BOC) 24 weeks 12 weeks in patients infected with G1b 12 weeks in patients infected with G1a* 12 weeks 12 weeks 24-48 weeks (incl. 12 weeks of TVR) 24 weeks (incl. 12 weeks of SMV) |
| **2**    |              | DCV + ASV, PTV/r/ObV + DSV, PTV/r/ObV + DSV, PTV/r/ObV + DSV + RBV, SOF + DCV, SOF + DCV + RBV, SOF/LDV, SOF + RBV, SOF + SMV +/- RBV | 24 weeks 12 weeks if F3, in patients infected with G1b 12 weeks if F4, in patients infected with G1b 12 weeks if F3, in patients infected with G1a* 24 weeks if F4, in patients infected with G1a* 12 weeks if F3 24 weeks if F4 12 weeks if F3; 24 weeks in F4 24 weeks 12 weeks |
| **3**    | Untreated patients | PegIFNα + RBV | 16-24 weeks |
| **4**    | Fibrosis at F1-F2 | DCV + PegIFNα + RBV, PTV/r/ObV + RBV, SMV + PegIFNα + RBV, SOF + DCV, SOF/LDV, SOF + PegIFNα + RBV | 24 weeks 12 weeks 24 weeks (incl. 12 weeks of SMV) 12 weeks 12 weeks 12 weeks |
| **5**    | Untreated patients and inefficacy of previous therapy | SOF + PegIFNα + RBV | 12 weeks |
| **6**    | Untreated patients and inefficacy of previous therapy | SOF + PegIFNα + RBV | 12 weeks |

*In patients infected with virus of an unknown genotype 1 subtype or with mixed genotype 1 infection the recommended treatment is the same as in patients infected with virus of genotype 1a*
Table 3. Contraindications to interferon α therapy

| Condition                                                                 |
|---------------------------------------------------------------------------|
| **Interferon α should not be used in the following cases:**               |
| History of hypersensitivity to interferons or any of the excipients     |
| Decompensated cirrhosis                                                  |
| Hepatitis or another disease with autoimmune aetiology                   |
| Post-transplantation status of liver or any other organ                  |
| Patients approved for liver transplantation                               |
| Severe, especially unstable heart disease whose difficult-to-control status was verified by a cardiologist |
| Metabolic syndrome and difficult-to-treat diabetes, following consultation with an endocrinologist |
| Depression, suicidal ideation or attempts documented by psychiatric evaluation |
| Thyroid diseases accompanied by abnormal TSH levels                     |
| Anaemia                                                                   |
| Absolute neutrophil count < 1,500/µl                                     |

Table 4. Interferon intolerance criteria

| Criterion                                                                 |
|---------------------------------------------------------------------------|
| Hypersensitivity to interferon or any of the excipients                  |
| Autoimmune disease                                                       |
| Exacerbation of a previously existing comorbidity                        |
| Decrease in initial body weight by more than 20%                          |
| Depression, suicidal ideation or attempts                                 |
| Thyroid function disorders                                                |
| Haemoglobin concentration < 8.5 mg%                                       |
| Thrombocytopenia < 50,000/µl                                              |
| Absolute neutrophil count < 500/µl                                       |

Therapy with boceprevir

Boceprevir treatment is preceded by four weeks of dual drug therapy, which is referred to as the lead-in phase. The therapy is based on one of PegIFNα in combination with RBV. Boceprevir should be added starting at week 5 of therapy [14].

Duration of treatment in previously untreated patients:
- 28 weeks (4 weeks of lead-in therapy + 24 weeks of triple drug therapy) if HCV RNA is not detectable in blood serum at weeks 8 and 24,
- 48 weeks (4 weeks of lead-in therapy + 32 weeks of triple drug therapy + 12 weeks of PegIFNα and RBV) if viraemia detected at week 8 of therapy becomes undetectable at week 24.

Duration of treatment in patients with a relapse of infection:
- 48 weeks (4 weeks of lead-in therapy + 32 weeks of triple drug therapy + 12 weeks of PegIFNα and RBV).
  Triple drug therapy with BOC should be discontinued in the following cases:
  - HCV RNA is ≥ 1000 IU/ml at week 8 of therapy,
  - HCV RNA is ≥ 100 IU/ml at week 12 of therapy,
  - HCV RNA is detectable (recommended limit of detection ≥ 25 IU/ml) at week 24 of therapy.

**Therapy with daclatasvir**

The daclatasvir (DCV) should be used in interferon-free therapy, in combination with sofosbuvir (SOF) for 12 weeks. In patients previously treated with a protease inhibitor the therapy should be extended to 24 weeks and the addition of RBV should be considered [15].

Daclatasvir can also be used in conjunction with asunaprevir (ASV) after the latter is approved for marketing in Poland [16, 17].

**Therapy with paritaprevir/ritonavir and dasabuvir**

Patients infected with HCV subgenotype 1b should take paritaprevir/ritonavir (PTV/rt/OBV) + dasabuvir (DSV) for 12 weeks. The regimen is complemented by RBV in patients infected with subgenotype 1a. The regimen recommended for patients infected with a virus of an unknown genotype 1 subtype or with mixed HCV G1 subtype is the same as for patients infected with HCV genotype 1a [18, 19].

**Therapy with telaprevir**

Triple drug treatment with telaprevir (TVR) can be considered in patients who have not been previously treated or have had a relapse of infection after ineffective PegIFNα + RBV therapy. Initially, patients should receive treatment in combination with PegIFNα and RBV for 12 weeks. Then, patients with undetectable viremia at weeks 4 and 12 of therapy should receive PegIFNα and RBV alone for another 12 weeks. Triple drug therapy with TVR should be discontinued if the concentration of HCV RNA exceeds 1,000 IU/ml at week 4 or 12 of treatment. In other patients, dual drug therapy should be continued until week 48. If viraemia is detectable at week 24 or 36, treatment must be discontinued [20].

**Therapy with sofosbuvir**

Triple drug therapy with SOF is used in combination with PegIFNα and RBV for 12 weeks [21]. The recommended duration of therapy with sofosbuvir combined with ledipasvir is 12 weeks in patients
who have not been treated before, and 24 weeks in other patients [22].

**Therapy with simeprevir**

Initially, patients should receive triple drug therapy with SMV in combination with PegIFNα and RBV for 12 weeks. Then, SMV is discontinued and patients are treated with PegIFNα and RBV alone for another 12 weeks. Triple drug therapy with SMV should be discontinued if HCV RNA is detectable at week 4 or 12 [23].

**Treatment of patients with advanced liver fibrosis (F3-F4) and contraindications to or intolerance of interferon**

The following therapeutic regimens are recommended:

- PTV/r/OBV + DSV – 12 weeks in patients infected with G1b, with fibrosis stage F3,
- PTV/r/OBV + DSV + RBV – 12 weeks in patients infected with G1b, with fibrosis stage F4 and compensated liver function,
- PTV/r/OBV + DSV + RBV – 12 weeks in patients infected with G1a (also in unspecified subtype 1 or mixed genotype 1 infections), with fibrosis stage F3,
- PTV/r/OBV + DSV + RBV – 24 weeks in patients infected with G1a (also in unspecified subtype 1 or mixed genotype 1 infections), with fibrosis stage F4 and compensated liver function,
- SOF + DSV – 12 weeks in patients with fibrosis stage F3,
- SOF + DSV + RBV – 24 weeks in patients with fibrosis stage F4,
- SOF/LDV – 12 weeks in patients with fibrosis stage F3,
- SOF/LDV – 24 weeks in patients with fibrosis stage F4 and compensated liver function,
- SOF/LDV + RBV – 24 weeks in patients with fibrosis stage F4 and compensated liver function,
- SOF + SMV +/- RBV – 12 weeks,
- SOF + RBV – 24 weeks if the combination of SOF with DCV or SMV is not possible.

Daclatasvir can also be used in combination with asunaprevir (DCV + ASV) after the drug is approved for marketing in Poland [16, 17].

**Infection with HCV genotype 2**

**Dual drug therapy with interferon**

PegIFNα combined with RBV should be used in previously untreated patients. The duration of treatment is 24 weeks, but it may be reduced to 16 weeks in patients with low baseline viraemia (<400,000 IU/ml) which is undetectable after 4 weeks of therapy. The treatment should be discontinued as ineffective if viraemia in the blood serum does not decrease by at least two logarithmic values (i.e. 100-fold) after 12 weeks of therapy.

**Therapy without interferon**

Sofosbuvir in combination with RBV should be used for 12 weeks only in the cases listed below:

- contraindications to or intolerance of interferon (see the Tables),
- inefficacy of prior PegIFNα + RBV therapy (relapse, partial or complete lack of response) in patients with advanced liver fibrosis (stages F3-F4),
- decompensated liver function.

The duration of treatment can be extended to 24 weeks in patients with cirrhosis (F4).

**Infection with HCV genotype 3**

**Dual drug therapy with interferon**

PegIFNα combined with RBV should be used in previously untreated patients. The duration of treatment is 24 weeks, but it may be reduced to 16 weeks in patients with low baseline viraemia (<400,000 IU/ml) which is undetectable after 4 weeks of therapy. The treatment should be discontinued as ineffective if viraemia in the blood serum does not decrease by at least two logarithmic values (i.e. 100-fold) after 12 weeks of therapy.

**Triple drug therapy with interferon**

The combination of PegIFNα, RBV and SOF should be used for 12 weeks in patients who have failed the dual drug regimen PegIFNα + RBV (relapse, partial or complete lack of response) and have low-stage liver fibrosis (F1-F2).

**Therapy without interferon**

SOF + RBV therapy should be used for 24 weeks in patients with contraindications to or intolerance of interferon and in patients with decompensated liver function.

24-week therapy based on the combination of SOF + RBV with LDV or DCV should be used in patients who have failed triple drug therapy or SOF + RBV or patients with advanced fibrosis (stages F3-F4).
Infection with HCV genotype 4

**Treatment of patients with mild liver fibrosis (F1-F2)**

**Therapy with daclatasvir**

Triple drug therapy with DVC in combination with PegIFNα and RBV should be used for 24 weeks if HCV RNA is undetectable at week 4 or 12 of therapy (recommended limit of detection < 15 IU/ml). If HCV RNA is detectable in any of these tests, treatment with PegIFNα and RBV alone should be continued for another 24 weeks.

The DVC + SOF combination can be used in interferon-free therapy for 12 weeks, but the treatment should be extended to 24 weeks in patients who have been previously treated with a protease inhibitor.

**Therapy with paritaprevir/r/ombitasvir**

Treatment with PTV/r/OBV in combination with RBV should be continued for 12 weeks.

**Therapy with sofosbuvir**

Triple drug therapy with SOF is used in combination with PegIFNα and RBV for 12 weeks. Interferon-free therapy based on the SOF/LDV combination should be continued for 12 weeks in previously untreated patients, and 24 weeks in patients who have failed prior therapy.

**Therapy with simeprevir**

Initially, patients should receive triple drug therapy with SMV in combination with PegIFNα and RBV for 12 weeks. Then, SMV is discontinued and patients are treated with PegIFNα and RBV alone for another 12 weeks. Triple drug therapy with SMV should be discontinued if HCV RNA is detectable at week 4 or 12 of treatment.

**Treatment of patients with advanced liver fibrosis (F3-F4) and contraindications to or intolerance of interferon**

The following therapeutic regimens are recommended:
- PTV/r/OBV + RBV – 12 weeks in patients with fibrosis stage F3,
- PTV/r/OBV + RBV – 24 weeks in patients with fibrosis stage F4 and compensated liver function,
- SOF + DCV – 12 weeks in patients with fibrosis stage F3,
- SOF + DCV + RBV – 24 weeks in patients with fibrosis stage F4,
- SOF/LDV – 12 weeks in patients with fibrosis stage F3,
- SOF/LDV – 24 weeks in patients with fibrosis stage F4 and compensated liver function,
- SOF/LDV + RBV – 24 weeks in patients with fibrosis stage F4 and decompensated liver function,
- SOF + SMV +/- RBV – 12 weeks.

Infection with HCV genotypes 5 and 6

**Triple drug therapy with interferon**

The combination of PegIFNα, RBV and SOF should be used as primary therapy for 12 weeks in all patients, both those who have not been previously treated and those who have failed prior therapy.

**Dual drug therapy without interferon**

The combination of SOF and RBV should be used for 24 weeks in patients with contraindications to or intolerance of interferon and liver fibrosis stages F3-F4, but also decompensated liver function.

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Table 5. Therapeutic options for patients prior to and after liver transplantation

| Genotype | Population | Drugs | Duration of therapy |
|----------|------------|-------|---------------------|
| 1, 2, 3, 4, 5, 6 | Approved for liver transplantation | SOF + RBV | Until transplantation, not longer than 24 weeks |
| 1, 4 | | PTV/OBV/r + DSV + RBV (G1) | 12 weeks in G1b infection (if Child-Pugh A; 24 weeks in G1a or G4 infection) |
| | | PTV/OBV/r + RBV (G4) | 24 weeks |
| | | SOF/LDV + RBV | 24 weeks |
| 1, 3, 4, 5, 6 | Post liver transplantation | SOF + DCV +/- RBV | 12-24 weeks |
| 2 | | SOF + RBV | 12-24 weeks |
| 1, 4 | | PTV/OBV/r + DSV + RBV (G1) PTV/OBV/r + RBV (G4) SOF/LDV + RBV SOF + SMV +/- RBV | 24 weeks 24 weeks 24 weeks 24 weeks |
Treatment of patients approved for liver transplantation or patients with recurrence of infection after liver transplantation

Patients who have been approved for liver transplantation or who have had a recurrence of infection after liver transplantation should only use interferon-free regimens listed in Table 5.

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20. Incivo, Charakterystyka Produktu Leczniczego.
21. Sovaldi, Charakterystyka Produktu Leczniczego.
22. Harvoni, Charakterystyka Produktu Leczniczego.
23. Olysio, Charakterystyka Produktu Leczniczego.