ENKORTEN® Summary Prospectus

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BOSNALIJEK
Health First!

HEADLINES

- A new combination medicine containing two immunomodulatory endogenous neuropeptides with anti-inflammatory effects: metenkefalin and tridecactide. Although the individual compounds as well as their effects in the body are already known, their combination and application in the therapy are innovative.
- **ENKORTEN®** has been registered for the treatment of autoimmune disease multiple sclerosis, its relapse-remitting form as the most common one. Clinical studies have shown promising results and a possible use of **ENKORTEN®** in treatment of some other auto-immune diseases such as asthma, as well as ulcerative colitis and Crohn's disease.
- Results of the recently completed clinical study of **ENKORTEN®** confirm its effectiveness and safety in improving the clinical condition of patients with moderate to severe forms of COVID-19 infection.
- **ENKORTEN®** is in the form of a lyophilisate for preparing a solution to be administered subcutaneously.
- Bosnalijek is looking for interested parties to acquire this medicine asset following its significant clinical development in the treatment of MS and, more recently, the effects of COVID-19.
- This asset will be of specific interest to an acquiring pharma or consortium of pharma that already operate in the MS and COVID-19 area, with an established extensive global distribution and internationally recognised brand to accelerate market launch and deployment.

DATA OBTAINED

during the possession period

In addition to clinical study (COVID-19), research work on the use of **ENKORTEN®** has been carried out and is currently in progress in the following therapeutic areas: relapsing-remitting multiple sclerosis (Phase III), bronchial asthma (Phase III), Crohn's disease (Phase II), ulcerative colitis (Phase II).

Pre-clinical studies carried out for: *systemic lupus erythematosus, rheumatoid arthritis.*

Phase I study, which was conducted on healthy volunteers was a first step in research of the use of **ENKORTEN®** in the above-mentioned the indications investigated to Phase III trials. Those results showed that **ENKORTEN®** is safe and very well tolerated when using a single dose, with no adverse effects recorded during this study. Safety profile is recognized as excellent in all other phases of clinical studies conducted. When it comes to diseases for which **ENKORTEN®** is approved or showed good therapeutic effects, safety is very important in terms of tolerability especially when compared to other therapies.

RECENT AND ONGOING STUDIES

Selected therapeutic areas and already performed studies are presented in the following sections. But before that, we would like to emphasize one recently finished and one ongoing clinical study:

- ***COVID-19***: A clinical trial to evaluate the efficacy and safety of immunomodulatory therapy (**ENKORTEN®**) for the treatment of patients with moderate to severe COVID-19. ***The study has been finalised, the report was prepared and sent to The Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina.*** The study is an open-label, prospective, randomized, comparative, multiple doses applied in addition to standard treatment of patients with moderate to severe COVID-19 infection.

- ***MS***: A multi-centre, international, randomized, blinded, parallel-group Phase IIIb study assessing the efficacy, safety, and tolerability of the neuropeptide combination (**ENKORTEN®**) compared to interferon beta-1a in patients with remitting multiple sclerosis.

COVID-19 STUDY

1.Inflammation

In response to infection, inflammation is the major physiological activated mechanism as the body's defense response. Depending on several factors involved in pathogenesis of an infection, inflammation can be localized and restricted to mild production of inflammatory cells or more systemic one, with much stronger immune response and production of inflammatory cells. In some cases, immune system overreacts with its inflammatory defense resulting in a storm of inflammation, which is caused by the major immune cells, so-called cytokines, involved in this process. It is called "cytokine storm".

Inflammation is a necessary evil if it is controlled and if it is mild to moderate. But an exaggerated, uncontrolled or irregular inflammation results in cytokine storm. The said cytokine storm, as pathophysiological mechanism of moderate to severe COVID-19 patients, is responsible for disease deterioration, progression and in the most severe cases, fatal outcome. Cytokine storm, as hyper-inflammation, can lead to multiorgan destruction and/or shock.

A powerful therapeutic mechanism for limiting a cytokine storm and regulating an exaggerated body's immune response is immunomodulation.

COVID-19 STUDY

1.Inflammation

ENKORTEN®, used for immunomodulation, targets the *cytokine storm* for therapeutic benefit. A complete blockage of cytokines and body's immune response is counterproductive and the action of **ENKORTEN®** is to immune-modulate, i.e. convert hyper-inflammation to a more balanced inflammation resulting in optimal immune defense for fight against coronavirus infection.

ENKORTEN® displays pharmacodynamic immunomodulatory activity, possibly shifting the immune response from active pro-inflammatory to regular. This is achieved via downregulation of certain classes of inflammatory mediators, i.e. primarily cytokine interleukin-6 (IL-6), as well as other initial mediators of inflammation.

The above-described action represents the primary rationale for using **ENKORTEN®** in therapies for patients with COVID-19, because it triggers a potential change in the immune response to alteration and/or inhibition of the «cytokine storm» and its potentially fatal consequences.

A clinical study was conducted with the aim of evaluating the safety and efficacy of **ENKORTEN®** as immune-modulator.

COVID-19 STUDY

2. Study Protocol Synopsis

Following the Research Protocol, **ENKORTEN®** is indicated for the treatment of patients of both genders with a moderate to severe COVID-19 infection, aged >18 years.

Hospitalized patients with laboratory-confirmed (PCR) COVID-19 infection, with a moderate to severe COVID-19 infection, with radiology-confirmed pneumonia within the clinical condition of COVID-19 infection including pulmonary opacity, with a clinical indication for pneumonia: increased body temperature (defined as a value above ≥ 36.6^{0}C axillary route, ≥ 37.2°C oral route or ≥ 37.8 °C rectal route) and/or dyspnoea and/or cough and/or SpO2 <96% are enrolled in the study. Patients with a mild COVID-19 infection, patients with malignant disease, severe liver and kidney insufficiency, patients under treatment with immunomodulatory or immunosuppressive agents, haloperidol or dopamine antagonists, or nonsteroidal anti-inflammatory drugs, except for paracetamol (acetaminophen), were under exclusion criteria.

All the patients received the standard therapy prescribed by the research centre's treatment protocol, and they were randomized into two groups: an experimental group receiving additionally **ENKORTEN®**, and the control group receiving only standard of care.

ENKORTEN® was applied as once daily dose of 12 mg for the first 7 days. After that, one day without **ENKORTEN®** was followed by one day when **ENKORTEN®** was applied as single dose of 12 mg. This method of application every second day was used for the next 14 days, or until discharge from the hospital.

COVID-19 STUDY

3. Analysis of **ENKORTEN®** efficacy and outcomes

The primary efficacy outcome was time to onset of improvement in the patient's clinical condition, and it was found that the **ENKORTEN®** group had a significantly shorter time to 7 and 14-day clinical improvement as compared to the standard therapy group.

Patients in **ENKORTEN®** group had significantly shorter time to 7-day clinical improvement [median 4.0 days, 95% CI (3.4-4.6)] than patients in the standard therapy group [median 6.0 days; 95% CI (4.9-7.1); log-rank p=0.004]. **ENKORTEN®** therapy was associated with significantly shorter 7-day clinical improvement compared to standard therapy group (HR=2.2; 95% CI (1.2-4.1); p=0.012).

In the severe disease stratum (47 patients), the median time to clinical improvement was 4 days; 95% CI (3.0-5.0) days, in **ENKORTEN®**, as compared with 7 days; 95% CI (5.6-6.8) days in the standard therapy group (log-rank p=0.046).

In the moderate disease stratum (63 patients), the median time to clinical improvement was 4 days; 95% CI (3.2-4.8) days in **ENKORTEN®**, as compared to 6 days; 95% CI (4.5-7.5) days in Standard therapy group (log-rank p=0.046).

ENKORTEN® therapy was associated with significantly shorter 14-day clinical improvement compared to the standard therapy group (HR=1.55; 95% CI (1.04-2.32); p=0.033).

COVID-19 STUDY

3. Analysis of **ENKORTEN®** efficacy and outcomes

In multivariate Cox regression analysis **ENKORTEN®** remained independently associated with a shorter time to clinical improvement during 7 days (HR=1.91; 95% CI (1.2-3.1; p=0.008) and 14 days (HR=1.64; 95% CI (1.1-2.5; p=0.022)), after controlling for the disease severity at admission as well as age, gender, time from symptoms onset to admission, azithromycin, chloroquine/hydroxychloroquine therapy, corticosteroid therapy.

Serum interleukin-6 (IL-6) levels significantly decreased both in **ENKORTEN®** group (p=0.011) and standard therapy group (p=0.048). Median change in serum IL6 levels was not significantly different between **ENKORTEN®** and standard therapy group (-12.9 (-36.6; -0.9) vs -24.7 (-58.3; -0.7) pg/mL; p=0.420).

Median change in Neutrophil/Lymphocyte ratio (NLR) from day 1 to day 7 was significantly different between **ENKORTEN®** and standard therapy group. Median NLR change from day 1 to day 7 significantly decreased compared to standard therapy group [-1.7 (-3.5; 0.1) vs. +0.02 (-2.0; 1.3); p=0.010]. Higher neutrophil-lymphocyte ratio (NLR) in control group compared to **ENKORTEN®** potentiates the symptoms' severity and thus the mortality rate of COVID-19. NLR has been shown to serve as a reliable indicator of severe COVID-19. Additionally, critically ill COVID-19 patients show higher NLR when compared with non-ICU patients. NLR is recognized as a useful systemic inflammation marker for screening COVID-19-infected patients and may be used as a useful predictor of a poor prognosis at the initial moment of hospitalization. As rapidly and easily measurable via the complete blood count, NLR is an inexpensive marker of systemic inflammation for the hospital clinical routine.

COVID-19 STUDY

3. Analysis of **ENKORTEN®** efficacy and outcomes

SAFETY RESULTS:

Safety and tolerability evaluation confirmed that **ENKORTEN®** has been well-tolerated. AEs registered during the use of **ENKORTEN®** were mild and usually linked to immediate use of the medicine. All AEs were short-lasting and reversible.

Monitoring of the clinical parameters (pulse, temperature, blood pressure) before and during the treatment has not shown significant deviations.

CONCLUSIONS:

In this study, the efficacy and safety of **ENKORTEN®** in the therapy of moderate and severe COVID-19 patients were confirmed.

Primary efficacy outcome was time to onset of improvement in the patient's clinical condition and it was found that **ENKORTEN®** group had significantly shorter time to 7 and 14-day clinical improvement compared to the standard therapy group.

Moreover, safety and tolerability evaluation included in the primary outcomes confirmed that the **ENKORTEN®** has been well-tolerated.

PREVIOUS STUDIES

Studies in multiple sclerosis

The purpose of Phase II and Phase III studies was to investigate the efficacy and safety of **ENKORTEN®** in the treatment of multiple sclerosis (MS). The studies enrolled patients diagnosed with the relapsing-remitting form of MS. In both phases, **ENKORTEN®** proved its efficacy and high safety profile.

Phase II clinical study's results demonstrated:

Relapses:

Number of relapses: Statistically significant reduction in number of relapses was noted in the experimental group compared to control group during the study.

Duration of relapse: In addition, duration of relapse state during the study was significantly reduced in experimental compared to control group.

Time to first relapse: Cumulative probability of the time to first relapse was statistically longer in patients taking **ENKORTEN®** (experimental group) compared to patients who were free from medication for MS (control group).

Number of relapse-free patient: 72% of patients in experimental and 42% in the control group remained relapse free throughout the study period of 12 months.

PREVIOUS STUDIES

Studies in multiple sclerosis

EDSS:

In the experimental group a significant decrease in the scores were noted, which reflects the improvement in the disability level. In contrast, statistically significant increase in EDSS was noted within the control group, which represents deterioration in the disability level. In addition, statistically significant difference in EDSS was noted between the control and experimental group when the difference in baseline EDSS was compared to EDSS measured at the end of the study (after 12 months).

MRI:

T2 lesions: statistically significant increase was found in the MRI T2 lesion number throughout the study (after 3, 6 and 12 months) compared to T2 lesion number measured before the study in the control group. In contrast, in experimental group statistically significant decrease in the T2 lesion number was noted for the first 6 months of the study (compared to baseline), which was lost for the last 6 months of the study. This points towards the dosage of 12 mg **ENKORTEN®** administered once a week (which was given for the last 6 months of the study) as not being sufficiently effective to keep reducing T2 lesion number. Statistically significant difference between control and experimental group was noted in the MRI T2 lesion load assessed as a difference in lesion number measured at the end of the study (after 12 months) and compared to baseline T2 lesion load.

No serious adverse effects were recorded during the research. All reported minor side effects were skin reactions at the injection site. The best response to therapy was observed in patients who received **ENKORTEN®** three times a week, and this therapy's protocol was further recommended.

PREVIOUS STUDIES

Studies in multiple sclerosis

Phase III research examined the efficacy and safety of **ENKORTEN®** in the treatment of multiple sclerosis. The included patients were diagnosed with the relapse-remitting form of MS. The research duration was 6 months.

RELAPSES:

- *Number of relapses:* a reduction of 63% in the number of relapses was seen in the Experimental group compared to the Control group during the study.
    - *Duration of relapse:* decreased by 67% in experimental compared to the control group.
    - *Time before the first relapse:* the time before the first relapse was longer in patients taking **ENKORTEN®** (experimental group) than in patients who had not been treated for MS (control group).
- *Number of relapse-free patients:* within six months, 85% of patients in the experimental group and 67% in the control group had no relapses. EDSS: A significant reduction in EDSS scores was noted in the experimental group, which reflects the improvement in the disability rate. In contrast, a statistically significant increase in EDSS scores was noted in the control group, which indicates an increase in the disability rate. Also, a statistically significant difference in EDSS scores was noted between the control and experimental group when the difference at baseline EDSS was compared to EDSS scores measured at the end of the study (after 6 months).

PREVIOUS STUDIES

Studies in multiple sclerosis

According to MRI data in the experimental group:

- T1 lesions: a statistically significant decrease in the average diameter of T1 lesions was noted in the experimental group during the study. A comparison of the control and experimental groups showed a good statistically significant tendency towards reducing maximum diameter, volume, and the number of T1 lesions in the experimental group compared to the control group. The size of T1 lesions (as represented by average diameter, maximum diameter, and volume) and the number of T1 lesions had a statistically decreasing tendency in patients taking **ENKORTEN®** compared to those who were medication-free (medication for MS).

- T2 lesions: a statistically significant reduction in size (mean diameter, maximum diameter, and volume) of T2 lesions in the experimental patient group was found when all the CNS sites studied were grouped for analysis. The number of T2 lesions in the experimental group has significantly decreased in the last three months of the study in the bilateral paraventricular region of the brain. Analysis of T2 lesions between the control and experimental group showed a statistically significant downward trend in the maximum diameter, volume, and the number of lesions at the end of the study compared to the control group.

The blood and urine safety parameters that were monitored during the study remained within normal range. No serious adverse effects were recorded during the study other than those locally related to the injection of **ENKORTEN®**.

PREVIOUS STUDIES

Studies in multiple sclerosis

Phase II research was to analyze the efficacy and safety of using **ENKORTEN®** in the treatment of bronchial asthma. The research duration was 12 weeks. A clinical study has shown the therapeutic efficacy of **ENKORTEN®** in the treatment of bronchial asthma. It was noted in the controlled group:

- *a significant improvement in respiratory insufficiency.*
- *the differences between the measured values of the forced expiratory volume in the first second (FEV1) were statistically significant (p = 0.0055) after 12 weeks of using **ENKORTEN®**.*
- *the difference in values of peak expiratory flow (PEF) in the experimental group was statistically significant (p=0,004) after 12 weeks of using **ENKORTEN®***
- *no statistically significant difference was registered in the control group in FEV1 and PEF values.*
- *a comparison of the standard treatment for bronchial asthma (topical medications from the beta-adrenergic receptor agonist group and corticosteroids) and **ENKORTEN®** demonstrated a lower need for standard medications for bronchial asthma treatment in the experimental group, and this is an additional beneficial effect of **ENKORTEN®**.*

Measured safety parameters (heamatological status, peripheral blood smear, catalytic concentration of hepatic and pancreatic enzymes, functional renal tests, serum and whole blood cholesterol and triglyceride levels) showed no deviations from the reference values.

No serious adverse effects were recorded during the research. Minor adverse effects were skin reactions at the injection site of **ENKORTEN®**.

Bosnalijek was established in 1951 and has since become the largest industrial manufacturer of medicines in Bosnia and Herzegovina.

The focus of the company's product range is on medicines for mass therapeutic application. The product range includes medicines for paroral, parenteral and topical administration with effect on the digestive system and metabolism, cardiovascular system, systemic infections, skin, musculoskeletal, the nervous and respiratory systems and several systemic hormonal medicines.

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