BRIEF INFORMATION ON WOBENZYM N

1. Name of the pharmaceutical agent
Wobenzym N enteric-coated tablets

2. Composition
2.1. Substance and indication group
- Antiphlogistic
- Fibrinolytic
- Immunotherapeutic agent

2.2. Effective components with regard to type and concentration
- 1 enteric-coated tablet contains:
  - 100 mg of pancreatin (equivalent to 300 proteases Ph. Eur. units)
  - 1 mg of chymotrypsin (equivalent to 5 µkat)
  - 45 mg of bromelain (equivalent to 225 FIP units)
  - 60 mg of papain (equivalent to 164 FIP units)
  - 50 mg of rutoside x 3 H2O

3. Fields of application
Thrombophlebitis. Inflammations of all types like, for example: Inflammation of the urinary and genital organs, inflammation of the veins, arteries and lymphatic vessels, inflammation associated with rheumatic illnesses, inflammation subsequent to such injuries as contusions, strains and sprains, inflammations of the skin like burns, abrasion, laceration and incision wounds, surgical wounds or varicose ulcers, inflammation following radiotherapy, and for prophylaxis against injuries, e.g. in sports.

4. Contraindications
Patients with severe congenital or acquired clotting disturbances (e.g. hemophilia, severe liver damage, dialysis patients) should be kept under careful control during therapy with Wobenzym N. The fibrinolytic effects of this agent must be taken into consideration when applying this agent during surgery.

5. Administration during pregnancy or while nursing
As with the use of other pharmaceutical preparations, the administration of Wobenzym N during pregnancy requires close cooperation with a physician.

6. Side effects
A sensation of fullness or flatulence and occasional cases of nausea are possible during the high-dose administration of Wobenzym N. In the event of such symptoms, the administration of this preparation should occur in divided doses to be given over the course of the day. Allergic reactions (rashes on the trunk) are only rare and subside rapidly after discontinuing the therapy. Harmless alterations in the consistency, color or odor of the stools may occur as a result of the enzymatic activity.

7. Drug interactions
The concomitant administration of Wobenzym N with antibiotics leads to an increased concentration of the antibiotics at their site of activity.

8. Precautions
None known.

9. Most important incompatibilities
None known.
10. Dosage and mode of administration
Should no other prescription be suggested, an individual of normal weight (70 kg) should receive an average daily dose of 2 enteric-coated tablets t.i.d. In special cases, during particularly severe states of an illness and in the event of injuries, as many as 30 enteric-coated tablets and more may be prescribed.

11. Duration and mode of application
The tablets should either be administered as a single dose or in the form of divided doses to be given over the course of the day. The tablets should be swallowed whole with abundant fluids and should be taken between the meals. The therapy is generally continued until the symptoms have subsided. Special considerations concerning sport's injuries, the inflammation of specific organs and rheumatoid arthritis:

A stosstherapy with 20 - 30 enteric-coated tablets given on day 1 to 3 and gradually reduced to an average maintenance dose of 2 enteric-coated tablets t.i.d. by day 10 is recommended in cases of acute injuries as, for example, with sport's injuries.

In cases of acute organ inflammation, or during vascular illnesses, 5 enteric-coated tablets t.i.d. are recommended for a period of 1 to 2 weeks. A reduction in the daily dose down to a maintenance dose may be carried out in the event of a clinical improvement. The duration of therapy is from 3 to 6 weeks.

Wobenzym N functions as a basic therapeutic agent for the treatment of rheumatoid arthritis and a dose of 24 - 32 enteric-coated tablets per day is prescribed during acute episodes. The dose can be reduced to 12 - 15 enteric-coated tablets daily in the event of an improvement in the subjective and objective parameters. Finally, a long-term therapy using 12 - 15 enteric-coated tablets per day should be carried out for a period of 4 to 6 months. A concomitant therapy with cortisone and non-steroidal antirheumatic agents may prove to be sensible initially. As soon as the pain and swelling is seen to improve, the dose of the non-steroidal antirheumatic agents and the cortisone may be reduced. A concomitant administration with other basic agents is not recommended.

12. Emergency measures, symptoms and antidotes
Even in the event of higher doses administered over longer time periods, no cases of intoxication have been noted to date. Nevertheless, a mild diarrhea may develop, although this disappears readily after discontinuing the administration of the preparation and without any additional treatment.

13. Pharmacological characteristics
The mixture as a whole, as well as the individual enzymes of bromelain, papain, trypsin, chymotrypsin and pancreatin, is effective in reducing the edemas associated with inflammation and the swelling, which stems from trauma (e.g. athletic injuries, surgery). This can be explained through the enzymatic proteolysis of macromolecules in the interstitial spaces as well as through the degradation of mediators (histamine, etc.).

Individual enzymes like bromelain, papain and trypsin demonstrate specific actions in in vitro systems like the inhibition of thrombocyte aggregation (bromelain) by way of a reduction in the ADP-dependent aggregability or the activation of plasminogen and degradation of the native fibrin (trypsin). The latter enzyme plays an important role in the region of the CH2 domains of the antibodies, which are already bound to an antigen. In illnesses caused by or associated with immune complexes, the immune complexes and the activation of the complement are consequently reduced. Similar effects are noted for bromelain and papain.

The extent to which proteases also have effects on structures, which are similar to the CH2 domains (e.g. regions of the adhesion molecules) is presently being investigated.

All of the proteases present in the preparation have an effect on the defense of the cells involved. Evidence of these effects has thus far been attained and demonstrated reliably, especially on macrophages/monocytes and NK cells. In the cytokine induction by the enzyme mixtures, it must be taken into consideration that the corresponding receptors are also susceptible to a modulation by the enzymes so that there may be a change in the resultant effects. In addition, the antiproteases, which are available for the transport of active proteases also have an effect on the respective systems. A reduction in their serum concentration through enzymes and their interactions with the enzymes is of additional importance in the sense of a regulatory effect on the immune system.

Anti-inflammatory characteristics have also been described for rutoside. Here, the inhibition of lipoxygenases and cyclooxygenases has been discussed as possible causative factors. The inhibition of thrombocyte aggregation has been demonstrated in experiments performed on rats as well. The causes of the vascular sealing and edema-protective effects of rutoside, however, are not yet known.
14. Toxicological characteristics
An acute mean lethal dose following oral application, however, could not be determined in various experimental animal studies. Investigations performed on combination preparations containing such components, as bromelain and trypsin, etc. have demonstrated no signs of toxicological characteristics. The results of chronic toxicity investigations obtained for a preparation containing bromelain and trypsin are also available. No findings, which differentiate from the norm, are to be seen following the daily administration of more than 450 mg of bromelain and 250 mg of trypsin. The findings are also negative for embryotoxicity and teratogenicity. A delay in fetal ossification was merely seen for a dose of 4 g/kg BW.

The toxicity of rutoside is considered to be low. In rats and mice, the administration of 0.2 to 0.5 g of rutoside/kg body weight resulted in no indications for an acute or chronic toxicity. Carcinogenicity and teratogenicity can be excluded for the oral administration of rutosides.

15. Pharmacokinetics
Macromolecular substances like the biocatalysts found in Wobenzym N enteric-coated tablets are resorbed through the gastrointestinal tract via various cell-mediated mechanisms and subsequently bonded to transport proteins (e.g. a1-antitrypsin, a2-macroglobulin). Following an individual dose, the maximum activity is attained 1 to 3 hours after administration (depending on the concentration) and is effective for up to 4 hours. The initial values are once again reached after 24 hours. Non-resorbed hydrolases and rutin components, which are not denatured or degraded, are ultimately eliminated with the stool.

Resorbed enzymes are eliminated in part by the cells of the mononuclear-phagocytic system. Rutosides given orally are found in the endothelium of the capillary system, where they can even be detected for a longer period of time. The half-life is thereby prolonged (> 24 hours). Rutosides undergo a first-pass effect through the liver. Furthermore, they pass through the enterohepatic circulation. The portion, which is not resorbed, is eliminated with the feces.

16. Bioavailability
The information concerning the bioavailability of this agent is practically useless because of the multiple interactions of the active components with endogenous substances and antiproteinases and since the proportions detected are either too high or too low depending on the particular determination method. According to the literature, the effective bioavailability of rutoside is 10 - 20%.

17. Other information
Because of its composition, Wobenzym N is not primarily analgetic, but rather antiedemic or, as a result of the rutoside, even edema protective. For this reason, the administration of this preparation to individual patients will not result in an immediate reduction in pain. Based on the mobilization and elimination of effective inflammatory substances from the sites of inflammation, an increase in the symptoms of pain may occasionally be seen which should consequently result in a reduction of the dose.

For diabetics: The carbohydrate contained in 1 enteric-coated tablet is equivalent to 0.015 carbohydrate units (0.18 g of carbohydrate)

18. Shelf life
The shelf life of Wobenzym N enteric-coated tablets is 2 years.