UNI-PHARMA
Pharmaceutical Laboratories S.A.

SUMMARY OF PRODUCT CHARACTERISTICS

(S P C)

ARTICLOX ®

Solution for injection 1mg/2ml AMP

Hydroxocobalamin acetate

1. PRODUCT NAME

ARTICLOX®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION (in active substance)

Each 2 ml ampoule contains 1mg hydroxocobalamin.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL DATA

4.1. Therapeutical Indications

- Megaloblastic anaemia due to B_{12} deficiency.
- Prophylactically to patients with total gastrectomy, total ileus resection, and total parenteral nutrition.

4.2. Dosage and Administration

For the treatment of megaloblastic anemia 1000μg (1000μg = 1mg) are administered to adults and children, per day, for 5 successive days (filling of depots) and after that 250 - 1000μg every month without interruption.

4.3. Contraindications

Hypersensitivity to cobalt or vitamin B_{12}.

Main "contraindication" is the unnecessary administration of this medicine.

4.4. Warnings and Precautions during Administration

❖ Don't use this medicine if there are particles suspended in the ampoule.

❖ Should only be administrated after confirmed diagnosis. During the therapy with **ARTICLOX®** hypokalemia may occur under increased needs of the erythrocytes and thus administration of potassium may be necessary.

❖ Due to the fact that vitamin B_{12} is a conditional growth factor of malignant cells vitamin B_{12} should be administrated with caution to patients with malignant tumors.

4.5. Drug Interactions

There isn't any known interaction with other medications until today. However you should inform your doctor for any other medication you take before you use this medicine.

4.6. Pregnancy and Lactation

Pregnancy

Category C:

Studies in animals have shown adverse effects on the fetus, but there are no adequate studies in pregnant women. The risk of using the medicine to the fetus may be acceptable because of the benefit for pregnant women.

Lactation

Vitamin B_{12} is excreted into breast milk in concentrations similar to its concentration in maternal blood.

4.7. Effect on the ability to drive or use machinery

The administration of the medication does not affect the ability to drive or use machinery.

4.8. Adverse Reactions

Almost none.

Rarely have been reported: Diarrhea, itching, anaphylaxis, general edema, pneumonic edema (at the beginning of the treatment).

4.9. Overdose

There isn't any known case of overdose until today.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

Therapeutical Category: Antianemic preparations (Treatment of megaloblastic anemia)

ATC Code: B03AB03

ARTICLOX® is a stable solution of Hydroxocobalamin. The therapeutic effects due to the extensive enrichment of the body with vitamin B_{12} and the continuous bound of the vitamin in the tissues at the injection site, achieve high concentrations in the blood and the substantial and continuous supply of the hepatic parenchyma. Due to these properties, the therapeutic results from the usage of **ARTICLOX®** are direct and stable, both in terms of suppression of pain and in protein synthesis (anabolic-stimulating activity).

5.2. Pharmacokinetic Properties

Absorption:

Intramuscular administration of hydroxocobalamin in healthy volunteers and individuals with vitamin B_{12} deficiency causes a greater increase in levels of serum cobalamin compared with the increase caused after the administration of similar dose of cyanocobalamin. Hydroxocobalamin is absorbed slower from the injection site, compared with cyanocobalamin and there are indications that the entry of hydroxocobalamin in the liver is more increased than cyanocobalamin. It is believed that the increased retention of hydroxocobalamin compared with that of cyanocobalamin is due to the higher affinity of the first with both the specific and the non-specific binding proteins in the blood and tissues, and the slower rate of absorption from the injection site.

Distribution:

Vitamin B_{12} is rapidly and extensively bound to specific plasma proteins-transporters called transcobalamins II. Smaller percentages bind to the storage proteins transcobalamin I (an alpha-glycoprotein) and transcobalamin III (an endo-alpha-glycoprotein). A small percentage of the vitamin can be found in free form or not extensively bound. The levels of blood transcobalamin II disappear after the absorption of vitamin B_{12}. Vitamin B_{12} is distributed in the liver, bone marrow and in other tissues, including placenta. At birth the concentration of vitamin B_{12} in the blood of the newborn is 3-5 times higher than those observed in maternal blood. Vitamin B_{12} is distributed into breast milk in concentrations similar to the concentrations in maternal blood. Total reserves of the body of vitamin B_{12} in healthy people ranging from 1-11mg, with a mean 5mg, located in the liver at a rate of 50-90%. In the liver, vitamin B_{12} is transformed into a coenzyme and probably in this form is stored in tissues.

Excretion:

The daily rate of consumption of vitamin B_{12} is 0.05-0.2% of the total depots of the body, ranging from 0.4-8mg, depending on the amounts of the depots. After injection of 50mg of vitamin B_{12}, 80-90% of the dose is retained in the body. With higher doses the rate of retention decreases rapidly and the size of the reduction varies between individuals. After I.M. administration of 0.5-1mg hydroxocobalamin, 16-66% of the dose excreted in urine. The greatest percentage is excreted within the first 24 hours. Approximately 10-15mg of vitamin

B_{12} is synthesized in the colon daily from bacteria but not absorbed and excreted unchanged in faeces.

5.3. Pre-clinical data relative to safety

Not applicable.

6. PHARMACEUTICAL DATA

6.1. Excipients

- Sodium chloride
- Sodium acetate
- Acetic acid
- Water for injection

6.2. Incompatibilities

None known.

6.3. Shelf Life

3 (three) years provided that the product is kept in its original packaging in accordance with storage conditions.

6.4. Storage

It is stored in airtight packaging, protected from light.

6.5. Packaging

Cardboard box that contains 3 ampoules of 2ml each, packaged in a blister pack from PVC and Aluminium foil, along with a Patient Information Leaflet.

6.6. **Administration Directions**

The content of the ampoule should not be used in case of the presence of particles.

6.7. **Marketing Authorization Holder**

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7. **MARKETING AUTHORIZATION NUMBER**

45550/9-9-2009.

8. **ISSUE DATE OF THE FIRST MARKETING AUTHORIZATION**

13.03.1997.

9. **DATE OF LAST REVISION**

22.04.2008.