CYANOCOBALAMIN 1 mg TABLETS
BIOWAIVER JUSTIFICATION

[redacted]

INTRODUCTION

Vitamin B_{12} (cobalamin) is a water-soluble vitamin that is crucial to normal neurologic function, red blood cell production, and DNA synthesis [redacted] Humans cannot produce vitamin B_{12} and it must therefore be regularly obtained from the ingestion of animal proteins or fortified cereal products. Dietary vitamin B_{12} is protein bound and must be split by proteolysis and gastric acid in the stomach. Free vitamin B_{12} is then attached to intrinsic factor, a glycoprotein secreted by the gastric mucosa. The vitamin B_{12}-intrinsic factor complex passes into the small intestine, where much of the complex is transiently bound to specific receptor sites in the wall of the lower ileum before the vitamin B_{12} portion is absorbed into the systemic circulation [redacted] This complex absorption mechanism limits the intestinal absorption of vitamin B_{12} from dietary sources to between 5 and 10 µg/day.

Vitamin B_{12} deficiency is a clinically important condition that occurs when vitamin stores are depleted through inadequate dietary intake or impaired absorption [redacted] Vitamin B_{12} is most abundant in foods of animal origin. Therefore, a diet low in animal products (e.g. vegetarian diets) and malabsorption associated with increasing age predispose to vitamin B_{12} deficiency. In addition, medications such as metformin and proton pump inhibitors have also been associated with vitamin B_{12} deficiency [redacted] Defective absorption is generally attributable to a specific failure of extraction and transport of vitamin B_{12} from dietary sources, as e.g. in patients with gastric achlorhydria and inadequate intrinsic factor production, or to more generalized disturbances of gastrointestinal structure and function, such as gastric resection, ileal resection, Crohn's disease, and bacterial overgrowth of the intestine. Autoimmune gastritis (pernicious anaemia) is the most common cause of severe vitamin B_{12} deficiency. Vitamin B_{12} deficiency causes reversible megaloblastic anaemia, demyelating neurologic disease, or both [redacted]

Supplemental vitamin B12, in the form of crystalline cobalamin (common forms include cyanocobalamin, methylcobalamin, and hydroxycobalamin), is administered either intramuscularly or orally to treat vitamin B12 deficiency. Unlike dietary vitamin B_{12}, which is protein bound and requires pepsin and acid conditions in the stomach for release and subsequent binding to intrinsic factor, crystalline cobalamin exists in the free unbound state. Studies have shown that 0.5 to 4% of radioactively labeled oral vitamin B_{12} can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia [redacted] High-dose oral vitamin B_{12} tablets (1000 µg to 2000 µg) taken daily are as effective as monthly intramuscular injections in correcting blood and neurologic abnormalities [redacted] Successful treatment of patients with B_{12} deficiency has been observed also with lower doses, but the proportion of patients responding decreases [redacted]

CYANOCOBALAMIN: PHYSICO-CHEMICAL PROPERTIES

Cyanocobalamin, a cyanoform of vitamin B12 which has now become the main mode of treatment for vitamin B12 deficiency, was first isolated in 1948 [redacted] Cyanocobalamin is the most widely used vitamer of vitamin B_{12} because it is the most stable of the vitamin B_{12} forms, and is easiest to crystallize and purify after it has been produced by bacterial fermentation or chemical synthesis (see molecular structure, fig. 1). Cyanocobalamin has a molecular weight of 1355.4 g/mol. It is sparingly soluble in water and its water solubility has been reported to be 12.5 mg/ml at 25 °C [redacted]

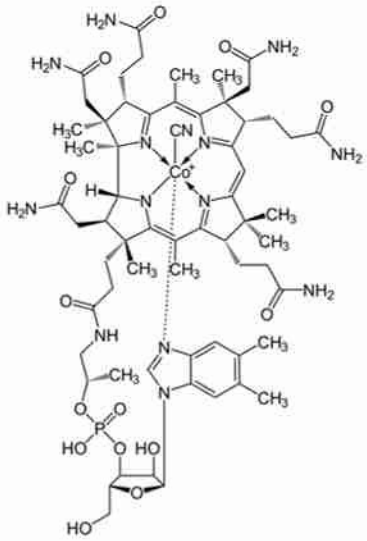

Figure 1. Molecular structure of cyanocobalamin.

CYANOCOBOLAMIN: BCS CLASSIFICATION

The highest administered dose according to the SmPC of Betolvex® 1 mg cyanocobalamin tablets, the marketed reference product, is 2 mg: "*Posology. Usually 2 tablets 2 times daily until full remission"* (Betolvex® 1 mg filmdragerade tabletter, Actavis Group hf. (IS), SmPC, 19/10/2014). [redacted] reported by [redacted] taking into account that they considered 1 mg to be the highest dose. Consequently, according to the Biopharmaceutics Classification System cyanocobalamin is a compound with high solubility [redacted]

Crystalline cobalamins are known to be absorbed by passive diffusion to the extent of ±1% over a range of ±100 µg to 5 mg [redacted] compared the pharmacokinetics of cyanocobalamin following oral administration of a new oral formulation versus a marketed 5 mg immediate release cyanocobalamin tablet [redacted] in healthy subjects. Four subjects received a single 1-mg IV dose of commercial cyanocobalamin. Consequently, the absolute bioavailability could be calculated for both the commercial 5 mg cyanocobalamin tablet and the new 5 mg cyanocobalamin formulation. The results showed an absolute bioavailability of 2.2% and 5.1% for the commercial and new 5 mg cyanocobalamin tablets, respectively. In addition, studies have shown that 0.5 to 4% of radioactively labeled oral vitamin B_{12} can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia [redacted] These data indicate that cyanocobalamin has a low permeability across the intestinal epithelium.

[redacted] Both the FDA and the EMA accept biowaivers for immediate release oral dosage forms if the following conditions are fulfilled:

The API (cyanocobalamin) should not have a narrow therapeutic index.

The daily requirement of vitamin B_{12} has been set at 2.4 µg, but higher amounts, i.e. 4 to 7 µg per day, are common intakes in persons who eat meat or take a daily multivitamin [redacted] Vitamin B_{12} has been demonstrated to be safe in doses up to 1,000 times the recommended dietary allowance and is safe in pregnancy [redacted]

[redacted] Safety does not appear to be an issue, as only mild adverse effects were reported from either the use of oral or intramuscular cyanocobalamin [redacted] Consequently, cyanocobalamin is not having a narrow therapeutic index.

The in vitro dissolution, carried out at pH 1.2, 4.5 and 6.8, should be very fast (i.e. more than 85% dissolved within 15 min) for both the test and reference product, OR the in vitro dissolution at pH 1.2, 4.5 and 6.8 should be fast (i.e. more than 85% dissolved within 30 min) and the profiles should be similar between the test and reference product.

The sponsor carried out in vitro dissolution tests on their product and on the Betolvex® reference product. These in vitro dissolution tests were carried out as recommended by the EMA Guideline for the Investigation of Bioequivalence [redacted]

The excipients used in the test product should be qualitatively the same as those in the reference product, and quantitatively similar.

The following excipients are present in the reference product: mannitol, pregelatinised starch, microcrystalline cellulose, magnesium stearate, stearic acid, potato starch, hypromellose, macrogol 400, titanium oxide (E171), erythrosine (E127), yellow iron oxide (E172). [redacted]

With the exception of potato starch, all other excipients used in the reference product were also used for the test product. [redacted] it concerns excipients that are commonly used, have a well known safety profile, and their quantities used are in line with the Inactive Ingredient Database of the FDA (http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm).

CONCLUSION

[redacted] In addition, cyanocobalamin (vitamin B_{12}) does not have a narrow therapeutic index. As a consequence, a biowaiver is appropriate from a biopharmaceutical point of view as well as from the perspective of public health.

[redacted]