2.5 CLINICAL OVERVIEW

2.5.1 Product development rationale

The objective of this report is to review the clinical data available in the public domain to determine whether there are any reasons, based on either the clinical data and/or on the findings of the pharmaceutical and preclinical expert reports, not to authorize Cyanocobalamin 50 mcg Tablets as essentially similar to brand Cytacon 50 micrograms Tablets containing Cyanocobalamin 50 micrograms manufactured Mercury Pharma Group Ltd, Capital House, 85 King William Street, London EC4N 7BL,UK accordance to Annex II of regulation 1084/2003/EC or 1085/2003/EC.

Cyanocobalamin 50 mcg Tablets has been filed as generic products, essentially similar to brand product Tablets under section 10(2)(b) of Directive 2001/83/EEC. Since the marketing authorization application is being made for a generic version of already existing medicinal product in market, no clinical studies except the bioequivalence study are carried out by the applicant.

2.5.2 Overview of Biopharmaceutics

An open-label, Randomized, single-dose, parallel group study was conducted by taking twenty healthy male subjects, aged 20 to 45 years, to compare the pharmacokinetics and tolerability of 2 oral formulation of Cyanocobalamin, a marketed Cyanocobalamin tablets {immediate release B 125 mg) and Cyanocobalamin formulated with a proprietary carrier, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC)-to established the feasibility of using an absorption enhancer with B12 to improve the uptake of vitamin.

Table-1: Pharmacokinetic parameters for non-baseline-corrected serum Cyanocobalamin following treatment-A, B, C and D

Pharmacokinetic Parameters	Treatment A* Mean (SD)	n	Treatment B† Mean (SD)	n	Treatment C‡ Mean (SD)	n	Treatment D§ Mean (SD)	n
C_{max}, pg/mL	28,175 (13,681)	4	12,847 (6613)	6	1239 (450)	6	221,287 (80,248)	4
T_{max}, h	0.54 (0.32)	4	0.50 (0.21)	6	6.83 (3.19)	6	0.05 (0.03)	4
$AUC_{0\text{-last}}$, pg/mL/h	127,494 (65,790)	4	54,609 (16,405)	6	23,165 (8382)	6	214,738 (44,614)	4
$AUC_{0-\infty}$, pg/mL/h	‖		‖		‖		235,165 (43,854)	3
K_e, 1/h	0.03 (0.010)	3	0.025 (0.009)	5	0.028 (0.006)	3	0.048 (0.018)	3
$t_{1/2}$, h	25.31 (8.8)	3	30.06 (8.24)	5	25.95 (6.07)	3	15.53 (4.70)	3

SNAC = sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.
*Treatment A: 2 × 5-mg cyanocobalamin/100-mg SNAC tablets.
†Treatment B: 1 × 5-mg cyanocobalamin/100-mg SNAC tablet.
‡Treatment C: 1 × 5-mg cyanocobalamin tablet.
§Treatment D: 1-mg cyanocobalamin IV (1 mg/mL solution).
‖Values missing or not reportable.

Based on data from treatment A, a 5-mg Cyanocobalamin dose was selected for use with treatments B and C. The oral Cyanocobalamin formulation containing SNAC had greater mean absolute bioavailability than the commercial oral formulation (5.09% vs 2.16%, respectively), calculated on AUC(0-last) values uncorrected for baseline, weight, or body mass index. It also had a reduced T(max) compared with the commercial formulation (0.5 hours vs 6.83 hours, respectively). The K(e) was similar between treatments (0.028 1/h vs 0.025 1/h). Comparable results were achieved using corrected values. The Cyanocobalamin/SNAC formulation was well tolerated, and there were no reported adverse events.

The result of the study concluded that an oral formulation of 5 mg Cyanocobalamin containing 100 mg SNAC, an absorption enhancer, provided significantly improved bioavailability and significant decrease in T max for B12 in a small study of normal healthy subjects compared with a commercial available 5 mg Cyanocobalamin oral formulation. Both oral formulations and commercial 1-mg Cyanocobalamin IV were well tolerated.

[redacted]

2.5.3 Overview of Clinical Pharmacology

Pharmacokinetics

A randomized, parallel-group, double-blind, dose-finding trial to determine the lowest oral dose of cyanocobalamin required to normalize biochemical markers of vitamin B (12) deficiency in older people with mild vitamin B(12) deficiency, defined as a serum vitamin B(12) level of 100 to 300 pmol /L (135-406 pg/mL) and a methylmalonic acid level of 0.26 mumol/L or greater. We assessed the effects of daily oral doses of 2.5, 100, 250, 500, and 1000 mug of Cyanocobalamin administered for 16 weeks on biochemical markers of vitamin B (12) deficiency in 120 people. The main outcome measure was the dose of oral Cyanocobalamin that produced 80% to 90% of the estimated maximal reduction in the plasma methylmalonic acid concentration.

Supplementation with Cyanocobalamin in daily oral doses of 2.5, 100, 250, 500, and 1000 mug was associated with mean reductions in plasma methylmalonic acid concentrations of 16%, 16%, 23%, 33%, and 33%, respectively. Daily doses of 647 to 1032 mug of cyanocobalamin were associated with 80% to 90% of the estimated maximum reduction in the plasma methylmalonic acid concentration.

The lowest dose of oral Cyanocobalamin required to normalize mild vitamin B(12) deficiency is more than 200 times greater than the recommended dietary allowance, which is approximately 3 mug daily.

[redacted]

Vitamin B12 is irregularly absorbed from the distal small intestine following oral administration. Dietary vitamin B12 is protein bound and this bond must be split by proteolysis and gastric acid before absorption. In the stomach, free vitamin B12 is attached to intrinsic factor; intrinsic factor a glycoprotein secreted by the gastric mucosa, is necessary for active absorption of the vitamin from the GI tract. The vitamin B12-intrinsic factor complex passes into the intestine, where much of the complex is transiently retained at specific receptor sites in the wall of the lower ileum before the vitamin B12 portion is absorbed into systemic circulation.

[redacted]

Following oral administration of vitamin B12 doses less than 3 ug, peak plasma concentrations are not reached for 8-12 hours because the vitamin is transiently retained in the wall of the lower ileum.

[redacted]

Vitamin B12 is distributed into the liver, bone marrow, and other tissues, including the placenta. At birth, the blood concentration of vitamin B12 in neonates is 3-5 times that in the mother. Vitamin B12 is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B12 concentration.

[redacted]

The daily turnover rate of vitamin B12 is 0.05-0.2% of total body stores, and may range from 0.4-8 µg, depending on the size of the storage pool. In healthy individuals receiving only dietary vitamin B12, about 3-8 µg of the vitamin is secreted into the GI tract daily, mainly via bile, with all but about 1 µg being reabsorbed; less than 0.25 µg of the vitamin is usually excreted in urine daily. When vitamin B12 is administered in amounts which exceed the binding capacity of plasma, liver, and other tissues, it is free in the blood and available for urinary excretion. Although about 80-90% of an initial injected dose up to 50 µg is retained by the body, with higher doses, the percent retained decreases rapidly and is subject to individual variation. Following IV or IM admin of 0.1-1 mg of Cyanocobalamin, 50-90% of the dose may be excreted in urine by glomerular filtration within 48 hours, with the major portion being excreted in the first 8 hours.

[redacted]

Vitamin B12 is actively transported to the fetus. This process is responsible for the progressive decline of maternal levels that occurs during pregnancy. Fetal demands for the vitamin have been estimated to be approx 0.3 microg/ day. Similar to other B complex vitamins, higher conctration of B12 are found in the fetus & newborn than in the mother. At term, mean vitamin B12 levels in 174 mothers were 115 pg/ml & in their newborns 500 pg/ml, a newborn: maternal ratio of 4.3. Comparable values have been observed by others. Mean levels in 51 Brazilian women, in their newborns, & in the intervillous space of their placentas were approx 340, 797, & 1074 pg/ml, respectively. The newborn: maternal ratio in this report was 2.3. The high levels in the placenta may indicate a mechanism by which the fetus can accumulate the vitamin against a concn gradient.

[redacted]

Vitamin B12 is excreted into human breast milk. In the first 48 hours after delivery, mean colostrum levels were 2431 pg/ml & then fell rapidly to concn comparable to those of normal serum. One group of investigators also observed very high colostrum levels, ranging from 6-17.5 times that of milk. Milk: plasma ratios are approx 1.0 during lactation. Reported milk concn of B12 vary widely. Mothers supplemented with daily doses of 1-200 microg had milk levels increase from a level of 79 to a level of 100 pg/ml. Milk concn were directly proportional to dietary intake. In a study using 8 mg/day supplements, mean milk levels of 1650 pg/ml at 1 week & 1100 pg/ml at 6 weeks were measured. Corresponding levels in unsupplemented mothers were significantly different at 1220 and 610 pg/ml, respectively.

[redacted]

This review apprises the reader of recent advances in cobalamin absorption and transport since 1970. This field has been of interest to gastroenterologists, hematologists, and biochemists as well as nutritionists. Clinical conditions leading to cobalamin deficiency present especially to the first two of these specialties. Many recent advances involve biochemical definition of the specific transport proteins themselves. Full understanding of the multiple clinical conditions associated with cobalamin deficiency requires some knowledge of these proteins. We do not discuss every paper in the field, especially the early literature (see 47, 61, 150). Despite rapid strides in understanding the mechanism of absorption and transport of cobalamin both in prokaryotic and eukaryotic cells, the complete sequence of events during cellular absorption at the plasma membrane level and events in the cells that mediate intracellular movement of cobalamin have not been elucidated completely. Here we emphasize the current state of knowledge about cobalamin absorption and transport in man and other mammalian systems, particularly the physiological role and biochemical nature of proteins involved (intrinsic factor, intrinsic factor-cobalamin receptor, transcobalamins).

The absorption of vitamin B12 appears to result from an orderly sequence of events. These events are shown in Table 1. The events before ileal absorption include: (1) the release of vitamin B12 from its binding by dietary protein, and the binding of B12 to R-protein in the stomach; (2) degradation of the R binder by pancreatic proteases and binding of B12 by intrinsic factor in the upper small bowel.

Table 1 *Phases of vitamin B_{12} absorption*

1	*Intragastric events*	
	a	Release of B_{12} from food proteins
	b	Binding of B_{12} by R-protein
2	*Duodenal and jejunal events*	
	a	Degradation of R-protein by pancreatic proteases
	b	Binding of B_{12} by intrinsic factor
3	*Ileal events*	
	a	Attachment of B_{12}-IF to receptor
	b	Transport of B_{12} across enterocyte
	c	Binding of B_{12} by transcobalamin II in portal blood
4	*Enterohepatic circulation*	
	a	Biliary excretion of B_{12} and B_{12}-analogues bound by R-protein
	b	Degradation of R-protein by pancreatic proteases and formation B_{12}-IF
	c	Ileal reabsorption of B_{12} and faecal excretion of B_{12}-analogues

It has been shown in vivo that there is a rapid release of vitamin B12 from food in the stomach. This release is facilitated by acids as well as pepsin. The dependence of this release on peptic digestion may, however, only apply to some food sources.

Cooking and food preparation may play a role, and from some food sources, including liver, vitamin B12 is readily released even when the pH of the stomach is neutral. It was thought until recently that vitamin B12, after its release from food proteins, attached to gastric intrinsic factor (IF). There is now evidence that cobalamins preferentially binds in the acid stomach to another

B12-binding protein, R-protein or haptocorrin. R-proteins are found in many body fluids including saliva, gastric juice, bile, intestinal juice, and serum.

[redacted]

Excretion of haptocorrin (R binder), cobalamin, and other corrinoids was studied in meconium from cystic fibrosis (n = 4), premature (n = 3), and control neonates (n = 13). Corrinoids content was 1.67 ± 0.92 pmol/mg protein in meconium of cystic fibrosis (CF) neonates but only 0.33 ± 0.37 and 0.48 ± 0.47 pmol/mg protein, respectively, in that of prematures and controls. Considering its molecular mass (110 100 ± 10 100) and its mean isoelectric point (3.67 ± 0.20), haptocorrin remained undegraded in the meconium of CF neonates whereas it was partially degraded in the meconium of prematures and in most of the meconium from controls. Sequestration of cobalamin by undegraded haptocorrin can explain its increased excretion in CF meconium. Cobalaminbinding capacity of haptocorrin was 22.13 ± 15.50 pmol/mg protein in CF meconium and about 400-fold lower in meconium of prematures and controls. This may correspond to a fetal intestinal hypersecretion in cases of CF.

[redacted]

Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (Cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

[redacted]

Absorption may be reduced by Para-aminosalicylic acid, colchinine, biguanides, neomycin, cholestyramine, potassium chloride, methyldopa, and cimetidine. Patients treated with chloramphenicol may respond poorly to this medicine. Serum levels of this medicine may be lowered by oral contraceptives. These interactions are unlikely to have clinical significance.

Anti-metabolities and most antibiotics invalidate vitamins B12 assays by microbiological techniques.

[redacted]

Pharmacodynamics

Mechanism of Action:

Cyanocobalamin stimulates reticulocytes, thus playing important role in hematopoiesis in that, together with folic acid, it is involved in formation of deoxyribonucleotides from ribonucleotides.

[redacted]

Vitamin B12 is converted to Coenzyme B12 in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. Vitamin B12 also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B12 is associated with fat and carbohydrate metabolism and protein synthesis.

[redacted]

Making Methionine

Vitamin B12 is called an enzyme cofactor because it's required for certain enzymes to function. One of these enzymes, methionine synthase, produces an essential amino acid called methionine that helps add a chemical group called a methyl group to more than 100 different compounds, including DNA, RNA and proteins. Your cells use methylation to activate genes, a process critical to hundreds of different cellular activities, to help RNA make new proteins in your cells and to manufacture certain hormones. Methylation of DNA and proteins keeps cells functioning normally, helping them to avoid becoming cancerous, according to the Linus Pauling Institute.

Producing Energy and Hemoglobin

Vitamin B12 also activates another enzyme, LmethylmalonylcoA mutase, that produces a compound called succinylCoA, which is crucial for the citric acid cycle. As part of a complex series of biochemical reactions, the citric acid cycle uses dietary carbohydrates, fats and proteins to produce ATP, an essential energy source for all cells. SuccinylCoA is also necessary for the production of hemoglobin in red blood cells. Hemoglobin is an iron containing protein that binds oxygen, carrying it in your blood to all your cells and organs. Vitamin B12 also takes part in production of myelin, the insulating sheath covering many nerves, but exactly how it does this isn't fully understood.

[redacted]

Imerslund-Gra¨sbeck syndrome (I-GS, megaloblastic anemia 1) is an autosomal recessive disorder characterized by intestinal cobalamin (vitamin B12) malabsorption and proteinuria. I-GS–causing mutations are found in either of 2 genes encoding the epithelial proteins: cubilin and amnionless (AMN). Cubilin recognizes intrinsic factor (IF)–cobalamin and various other proteins to be endocytosed in the intestine and kidney, respectively, whereas the function of AMN is unknown. Here we show that cubilin and AMN colocalize in the endocytic apparatus of polarized epithelial cells and copurify as a tight complex during IF-cobalamin affinity and nondenaturing gel filtration chromatography.

In transfected cells expressing either AMN or a truncated IF-cobalamin–binding cubilin construct, neither protein alone conferred ligand endocytosis. In cubilin transfectants, cubilin accumulated in early biosynthetic compartments. However, in cells cotransfected with AMN and the cubilin construct, cubilin trafficked to the cell surface and endosomes, and the cells exhibited IF-cobalamin endocytosis and lysosomal degradation of IF. These data indicate that cubilin and AMN are subunits of a novel cubilin/AMN (cubam) complex, where AMN binds to the aminoterminal third of cubilin and directs subcellular localization and endocytosis of cubilin with its ligand. Therefore, mutations affecting either of the 2 proteins may abrogate function of the cubam complex and cause IG-S.

[redacted]

[redacted]

Cellular entry and exit of cobalamin (cbl) is a complex process. The story of cbl and its relation to anemia has been known for 50 years, but the slow unravelling of the complexities related to intracellular trafficking has been mainly due to a variety of reactions involved, complexity of cbl structure and the possible influence of structure on binding to intracellular proteins and hence on cellular entry and exit, and to the extremely low levels of tissue proteins which delayed their isolation. Now that all the binding proteins, and their receptors are isolated, and our knowledge in cell biology of intracellular trafficking has greatly increased the future of cbl research appears to be bright. It is hoped that a total picture on the cellular movement and turnover of cbl and its analogs will help in a clearer understanding of the pathogenesis in some forms of cbl deficiency.

[redacted]

A study was conducted to determine the magnitude and mechanism of the reduction in serum vitamin B12 after Metformin administration. A comparative study design was employed using 2 groups (Metformin and control). A total of 21 patients with type 2 diabetes received sulfonylurea therapy; 14 of these 21 patients were switched to Metformin. Monthly serum total vitamin B12 measurements and holotranscobalamin (holoTCII) (B12-TCII) were performed. After 3 months of Metformin therapy, oral calcium supplementation was administered.

Serial serum vitamin B12 determinations revealed a similar decline in vitamin B12 and holoTCII. Oral calcium supplementation reversed the Metformin-induced serum holoTCII depression. Patients receiving Metformin have diminished B12 absorption and low serum total vitamin B12 and TCII-B12 levels because of a calcium-dependent ileal membrane antagonism, an effect reversed with supplemental calcium.

[redacted]

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12.

Folic acid is not a substitute for vitamin B12 although it may improve vitamin B12-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B12-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

Anaphylactic shock and death have been reported after parenteral vitamin B12 administration. No such reactions have been reported in clinical trials with Cyanocobalamin Tablets.

Blunted or impeded therapeutic response to vitamin B12 may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

Persons taking most antibiotics, methotrexate or pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays. Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B12.

[redacted]

2.5.4 Overview of Efficacy

A study was conducted to compare the efficacy of sublingual and oral administration of 500 µg of cobalamin in subjects with cobalamin deficiency. Thirty subjects with low serum concentrations of cobalamin participated in the study. Subjects were randomly allocated to receive one tablet daily of 500 µg cobalamin sublingually or orally, or two tablets daily of a vitamin B complex. Serum cobalamin concentrations before treatment were 94 ± 30 pmol l^{-1}, 108 ± 17 pmol l^{-1} and 98 ± 14 pmol l^{-1} in the sublingual B12, oral B12 and oral B-complex groups, respectively. After 4 weeks, concentrations rose to 288 ± 74 pmol l^{-1}, 286 ± 87 pmol l^{-1} and 293 ± 78 pmol l^{-1}, respectively. The increase in each group across time was statistically significant ($P = 0.0001$, differences [95% confidence intervals] 194.2 (114.5, 273.9), 178.3 (104.2, 252.4), and 195.1 (135.0, 255.2) pmol l^{-1}, respectively). There was no significant difference in concentrations between the treatment groups. A dose of 500 µg of cobalamin given either sublingually or orally is effective in correcting cobalamin deficiency.

[redacted]

A study was conducted to identify randomized controlled trial (RCT) evidence for the effectiveness of oral versus intramuscular vitamin B12 to treat vitamin B12 deficiency. We conducted a systematic review searching databases for relevant RCTs. Outcomes included levels of serum vitamin B12, total serum homocysteine and methylmalonic acid, haemoglobin and signs and symptoms of vitamin B12 deficiency.

Result of study shows that two RCTs comparing oral with intramuscular administration of vitamin B12 met our inclusion criteria. The trials recruited a total of 108 participants and followed up 93 of these from 90 days to 4 months. In one of the studies, mean serum vitamin B12 levels were significantly higher in the oral (643 ± 328 pg/ml; n = 18) compared with the intramuscular group (306 ± 118 pg/ml; n = 15) at 2 months ($P < 0.001$) and 4 months (1005 ± 595 versus 325 ± 165 pg/ml; $P < 0.0005$) and both groups had neurological responses. In the other study, serum vitamin B12 levels increased significantly in those receiving oral vitamin B12 and intramuscular vitamin B12 ($P < 0.001$).

The evidence derived from these limited studies suggests that 2000 mg doses of oral vitamin B12 daily and 1000 mg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term haematological and neurological responses in vitamin B12-deficient patients.

[redacted]

An intervention study in order to establish the efficacy of a supplement providing 500 µg Cyanocobalamin for four weeks in sixty-four institutionalized elderly residents, over 60 years of age, in Madrid (Spain). Before and after treatment, concentrations of serum cobalamin, serum holotranscobalamin, serum total homocysteine, and serum and red blood cell folate were analyzed. Clusters were built according to the initial cobalamin status and differences in the effect of supplementation were checked using a general linear model for repeated measures.

Cobalamin and holotranscobalamin increased highly significantly from 308 to 558 pmol/L and from 54 to 96 pmol/L ($p < 0.001$) in the whole study group as well as in each subgroup (clustered by initial cobalamin levels, all $p < 0.01$), with the highest relative change in the subgroup with the lowest initial cobalamin values. Total homocysteine decreased from 15 to13 µmol/l, $p < 0.001$). Only the change of cobalamin ($F = 4.61$, $p < 0.01$), but not of holotranscobalamin nor total homocysteine, depended on the initial serum cobalamin status. A supplementation with an oral supplement solution of 500 µg Cyanocobalamin daily for only four weeks, a shorter period than that found in former studies, may be considered suitable in institutionalized elderly.

[redacted]

A study was conduted to compare the efficacy and safety profile of a new proprietary oral vitamin B12 formulation (oral B12) with intramuscular (IM) vitamin B12 (IM B12) in restoring normal serum B12 concentrations in patients with low cobalamin levels (<350 pg/mL).

Patients were recruited from 5 centers and randomly assigned to receive oral B12 1000 µg, taken daily for 90 days, or IM B12 1000 µg, given on study days 1, 3, 7, 10, 14, 21, 30, 60, and 90. The patients were aged ≥ 60 years or aged ≥ 18 years and had gastrointestinal abnormalities or were on a restricted diet. The primary efficacy outcome compared the proportion of patients in each treatment arm in whom cobalamin levels were normalized (≥350 ng/mL) following 60 days of treatment. Secondary objectives included comparing the efficacy of the 2 formulations after 90 days of treatment, assessing time to normalization of B12 levels, and evaluating the changes in

the levels of biomarkers methylmalonic acid (MMA) and homocysteine (HC). The effect on holotranscobalamin I (active B12) levels was assessed as an exploratory end point and correlated to serum cobalamin levels in both treatment groups. Blood samples were collected at baseline (Day 1) and on days 15, 31, 61, and 91.

In this selected study population comprising individuals with low cobalamin levels hut who otherwise were in good health, patients received oral B12 (1000 µg/d) or IM B12 (1000 µg in 9 Injections over 3 months) for a total of 3 months. Both the oral and IM formulations were effective in restoring normal levels of serum cobalamin in all patients studied (100%). Both formulations used in this study were well tolerated at the dose studied.

[redacted]

A study was conducted to assess the effect of supplementation with 1000g crystalline cobalamin, carried either by a milk product or a capsule, on cobalamin status in mildly cobalamin-deficient elderly Dutch persons.

Two double-blind randomized controlled intervention studies, each covering a 12-wk supplementation period, were carried out in parallel. Mildly cobalamin-deficient elderly persons (n=112) were separately recruited for the milk and capsule trials. Mild cobalamin deficiency was defined as a cobalamin concentration between 100 and 300 pmol/L and a plasma methylmalonic acid (MMA) concentration 0.30 mol/L. Allocation to the placebo or cobalamin carrier was carried out independently in both trials.

In the fortified-milk group, the mean (± SD) increase in serum cobalamin was 250 ± 96 pmol/L, the median (5th and 95th percentiles) decrease in plasma MMA was 0.19 (- 0.76, - 0.04) mol/L, and the median decrease in plasma homocysteine was 4.0 (-7.3, 3.0) mol/L. All changes were significantly different from those in the placebo milk group ($P > 0.01$). Likewise, in the cobalamin-capsule group, the mean increase in serum cobalamin was 281 ± 136 pmol/L, the median decrease in plasma MMA was 0.18 (- 2.95, 0.14) mol/L, and the median decrease in

plasma homocysteine was 1.8 (- 10.6, 2.4) mol/L; all changes were significantly different from those in the placebo capsule group ($P > 0.01$). No significant differences were observed between the fortified-milk and capsule groups ($P > 0.40$).

Crystalline cobalamin added to milk is an effective alternative to cobalamin capsules for improving cobalamin status.

[redacted]

This is a Phase 3, open-label, single-center, 8-week study evaluating 50mcg daily intranasal Cyanocobalamin in patients previously maintained on monthly intramuscular B 12 injections. The primary endpoint of the study was the ratio of post-treatment B 12 levels relative to baseline B 12 levels.

Study population: Subjects enrolled in the study were age 18 - 85 years who required B 12 injections to maintain normal serum B12 levels. All subjects were on a stable maintenance dose of vitamin B 12 with trough serum B 12 levels in the normal range at the time of enrollment.

Study treatments: In this open-label trial, all patients received a total dose of 50 mcg Cyanocobalamin daily for eight weeks, delivered as two puffs of 25 meg Cyanocobalamin - one in each nostril daily. Treatment compliance was measured by patient diary recordings.

Efficacy measures: Efficacy measures included serum vitamin B 12 and homocysteine levels at 2, 4, 6, and 8 weeks after study drug initiation. Methylmalonic acid levels were measured at baseline and Week8.

Conclusions: Treatment with CaloMist (Cyanocobalamin) nasal spray 50 mcg daily (one 25 mcg spray in each nostril) was effective at maintaining vitamin B 12 levels in patients with vitamin B 12 deficiency previously normalized on IM B 12 injections. No data is available to evaluate the efficacy of this B 12 preparation for the treatment of B 12 deficiency in patients previously untreated.

[redacted]

2.5.5 Overview of Safety

Cyanocobalamin has been marketed in the United States since 1942 and the safety of Cyanocobalamin is well established. While the excipient profile for this drug product differs from that of the currently available B 12 nasal spray agent, it is almost identical to the currently available over-the-counter OCEAN premium nasal spray product. Therefore, the adverse event profile of the study drug in Study PR99-063as well as the postmarketing adverse event reporting for both Cyanocobalamin products and OCEAN Premium Nasal Spray were evaluated in the safety review.

Study PR99-063:

Disposition and exposure: All 25 subjects who received study drug completed the trial Overall, 96% of subjects took 80- 100% of their prescribed dose of *50* mcg daily. In one subject, the dose of study drug was increased to 100 mcg daily.

Deaths, serious adverse events, and adverse events leading to withdrawal: No deaths during this 8 week study. There was one serious adverse event reported- a 51 year-old woman was diagnosed with inter vertebral disc protrusion on Day 52. She was treated with surgery and subsequently completed the study. There were no adverse events leading to withdrawal during this 8-week study.

Adverse events: Overall, seventeen (68%) subjects reported at least one adverse event. The most common adverse events were nasopharyngitis, arthralgia, dizziness, headache, and rhinorrhea - each were reported by three (12%) subjects. Adverse events reported by two (8%) subjects included pain, bronchitis, pain in extremity, nasal discomfort, and rash. No new safety signals were noted in this small trial.

Laboratory evaluations: Hematology parameters were the only laboratory safety assessments performed. A complete blood count was assessed at Visits 1 and 6. As outlined in [redacted] review, there were no clinical relevant changes in hematology parameters.

Vital Signs: There were no clinically significant changes in vital signs, which were assessed at Visits 1 and 6, in this study.

Cyanocobalamin Post marketing Reports: Ass outlined in his review, [redacted] identified several post marketing reports of angioedema and angioedema-like events occurring with

Cyanocobalamin use. I agree with him that these events should be added to the cyanocobalamin labels.

OCEAN Premium Nasal Spray Post marketing Reports: OCE Premium Saline Nasal Spray has been manufactured and marketed for more than three decades, as a non-sterile, non-medicated isotonic aqueous moisturizing nasal spray. As outlined in the table below, there have been a very small number of patient complaints of adverse reactions (0.000 1%). The most common adverse reactions are nasal irritation and allergic symptoms.

[redacted]

The data described below and in Table 1 reflect exposure in 25 subjects (age range 27-82 years; 17 women; 21 Caucasians) with vitamin B12 deficiency (12 with pernicious anemia, 4 secondary to gastrointestinal surgery, 9 with unknown cause) who received CaloMist Nasal Spray 50 mcg daily for 8 weeks in an uncontrolled clinical trial. Prior to enrollment, all subjects were required to have normal vitamin B12 levels with intramuscular vitamin BI2 injections. One patient who completed the study developed epistaxis on Day 12 of dosing and was noted to have irritation of the right nasal septum at study end. This patient had pre-existing allergic rhinitis and required a doubling of the CaloMist Nasal Spray dose during the last week of the study because of declining vitamin B12 concentrations.

Table 1. Potentially related adverse reactions reported during 8 weeks of treatment with CaloMist Nasal Spray in an uncontrolled clinical trial.

PREFERRED TERM	CALOMIST NASAL SPRAY (CYANOCOBALAMIN) (N=25) N (%)
Arthralgia	3 (12%)
Dizziness	3 (12%)
Headache	3 (12%)
Nasopharyngitis	3 (12%)

Rhinorrhea	3 (12%)
Bronchitis	2 (8%)
Nasal Discomfort	2 (8%)
Pain	2 (8%)
Rash	2 (8%)
Asthma	1 (4%)
Back Pain	1 (4%)
Cough	1 (4%)
Epistaxis	1 (4%)
Hypersomnia	1 (4%)
Influenza Like Illness	1 (4%)
Malaise	1 (4%)
Pharyngolaryngeal Pain	1 (4%)
Postnasal Drip	1 (4%)
Procedural Pain	1 (4%)
Pyrexia	1 (4%)
Scab	1 (4%)
Sinus Headache	1 (4%)
Sinusitis	1 (4%)
Tooth Abscess	1 (4%)

Experience with Parenteral Vitamin B12

The following adverse reactions have been reported with parenteral vitamin B12:

Generalized: Anaphylactic shock and death

Cardiovascular: Pulmonary edema and congestive heart failure early in treatment Peripheral vascular thrombosis

Hematological: Polycythemia vera

Gastrointestinal: Mild transient diarrhea Dermatological: Itching; transitory exanthema

Post marketing Experience

The following adverse reactions have been identified during postapproval use of Cyanocobalamin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Angioedema and angioedemalike reactions

[redacted]

Laboratory Tests: During the initial treatment of patients with pernicious anemia, serum potassium must be observed closely the first 48 hours and potassium replaced if necessary.

Hematocrit, reticulocyte count, vitamin B12 , folate and iron levels should be obtained prior to treatment. Hematocrit and reticulocyte counts should be repeated daily from the fifth to seventh days of therapy and then frequently until the hematocrit is normal. If folate levels are low, folic acid should also be administered. If reticulocytes have not increased after treatment or if reticulocyte counts do not continue at least twice normal as long as the hematocrit is less than 35%, diagnosis or treatment should be reevaluated. Repeat determinations of iron and folic acid may reveal a complicating illness that might inhibit the response of the marrow.

Patients with pernicious anemia have about 3 times the incidence of carcinoma of the stomach as the general population, so appropriate tests for this condition should be carried out when indicated.

Drug/Laboratory Test Interactions: Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays.

Colchicine para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B12.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential have not been done. There is no evidence from long-term use in patients with pernicious anemia that Cyanocobalamin is carcinogenic. Pernicious anemia is associated with an 12 increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with Cyanocobalamin

Pregnancy: Teratogenic Effects. Pregnancy Category C: Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B 12 is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B12 that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 mcg daily) should be consumed during pregnancy.

Nursing Mothers: Vitamin B 12 is known to be excreted in human milk. Amounts of vitamin B12 that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women (4 mcg daily) should be consumed during lactation.

Pediatric use: Intake in children should be in the amount (0.5 to 3 mcg daily) recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

Adverse reactions:

Generalized: Anaphylactic shock and death have been reported with administration of parenteral vitamin B12.

Cardiovascular: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

Hematological: Polycythemia vera

Gastrointestinal: Mild transient diarrhea

Dermatological: Itching; transitory exanthema

Miscellaneous: Feeling of swelling of entire body

[redacted]

A study was conducted to evaluate the use of a combination of vitamins B1, B6, and B12 with dexamethasone in the treatment of the signs and symptoms of inflammatory neuropathy of the upper and lower limbs, in an open-label clinical trial. Patients were submitted to a 9-day treatment period with three doses of study medication at three day intervals, and a series of clinical and laboratory assessments, prior to the first dose of study medication and at each of the following three visits to the study center. Efficacy evaluations at each study visit included a 100mm VAS pain scale and global and satisfaction surveys completed by the patient and the investigating physician.

Safety evaluations included a comparison of changes in laboratory evaluations at each visit and the incidence, severity, duration, and outcome of adverse events. A total of sixty-one patients were enrolled in the trial. A clinically significant improvement in all of the efficacy measures was observed from the pre-treatment to end-of-study evaluations. No clinically significant alterations in clinical assessments were observed during the treatment period. Based on the results of this clinical study, we conclude that the combination of dexamethasone with the B-vitamins is safe and effective in the treatment of the signs and symptoms of inflammatory neuropathy.



A study was conducted to determine the efficacy and safety of the therapeutic combination of 10 mg piroxicam, 1 mg dexamethasone, 35 mg orphenadrine citrate, and 2.5 mg Cyanocobalamin (Rheumazin®) when compared with 20 mg piroxicam alone (Feldene®) in mandibular third molar surgery. Eighty patients scheduled for removal of the third molar were included in this randomized and double-blind study. They received (vo) Rheumazin or Feldene 30 min after tooth extraction and once daily for 4 consecutive days. Pain was determined by a visual analogue scale and by the need for escape analgesia (paracetamol). Facial swelling was evaluated with a measuring tape and adverse effects and patient satisfaction were recorded. There was no statistically significant difference in facial swelling between Rheumazin and Feldene (control group). Both drugs were equally effective in the control of pain, with Rheumazin displaying less

adverse effects than Feldene. Therefore, Rheumazin appears to provide a better risk/ benefit ratio in the mandibular molar surgery. Since the side effects resulting from nonsteroidal anti-inflammatory drug administration are a severe limitation to the routine use of these drugs in clinical practice, our results suggest that Rheumazin can be a good choice for third molar removal treatment.



2.5.6 Benefits and Risks Conclusions

Vitamin B12 (or Cyanocobalamin, CNCbl) was discovered exactly 60 years ago in the laboratories of Folkers and Smith as the anti-pernicious anemia factor, and its structure was revealed a few years later by the crystallographic studies in the Hodgkin laboratory. B12 is one of the most complex cofactors in nature and belongs to the family of tetrapyrrolic-derived macrocyclic compounds.

Various clinical studies are conducted to predict different Biopharmaceutics, clinical pharmacology, efficacy and safety of Cyanocobalamin and to provide an overall appraisal of the benefits and risks of its use in clinical practice.

An open-label, Randomized, single-dose, parallel group study was conducted by taking twenty healthy male subjects, aged 20 to 45 years, to compare the pharmacokinetics and tolerability of 2 oral formulation of Cyanocobalamin, a marketed Cyanocobalamin tablets {immediate release B 125 mg) and Cyanocobalamin formulated with a proprietary carrier, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC)-to established the feasibility of using an absorption enhancer with B12 to improve the uptake of vitamin and the result of the study concluded that an oral formulation of 5 mg Cyanocobalamin containing 100 mg SNAC, an absorption enhancer, provided significantly improved bioavailability and significant decrease in T max for B12 in a small study of normal healthy subjects compared with a commercial available 5 mg Cyanocobalamin oral formulation. Both oral formulations and commercial 1-mg Cyanocobalamin IV were well tolerated.

Different clinical studies are conduted to evaluate critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD) properties of Cyanocobalamin.

A randomized, parallel group, double blind, dose finding trial to determine the lowest oral dose of Cyanocobalamin required to normalize biochemical markers of vitamin B(12) deficiency in older people with mild vitamin B(12) deficiency and it was reported that the lowest dose of oral Cyanocobalamin required to normalize mild vitamin B(12) deficiency is more than 200 times greater than the recommended dietary allowance, which is approximately 3 mug daily.

Vitamin B12 is irregularly absorbed from the distal small intestine following oral administration. Dietary vitamin B12 is protein bound and this bond must be split by proteolysis and gastric acid before absorption. In the stomach, free vitamin B12 is attached to intrinsic factor; intrinsic factor a glycoprotein secreted by the gastric mucosa, is necessary for active absorption of the vitamin from the GI tract.

Following oral administration of vitamin B12 doses less than 3 µg, peak plasma concentrations are not reached for 8-12 hours because the vitamin is transiently retained in the wall of the lower ileum.

Vitamin B12 is distributed into the liver, bone marrow, and other tissues, including the placenta. At birth, the blood concentration of vitamin B12 in neonates is 3-5 times that in the mother. Vitamin B12 is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B12 concentration.

Vitamin B12 is actively transported to the fetus. This process is responsible for the progressive decline of maternal levels that occurs during pregnancy. Fetal demands for the vitamin have been estimated to be approx 0.3 microg/ day.

Vitamin B12 is excreted into human breast milk. In the first 48 hours after delivery, mean colostrum levels were 2431 pg/ml & then fell rapidly to concentration comparable to those of normal serum.

Pharmacokinetics interactions with other medicinal products may occur in case of Cyanocobalamin tablets and same has been reported in case of Omeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (Cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Absorption may be reduced by Para-aminosalicylic acid, colchinine, biguanides, neomycin, cholestyramine, potassium chloride, methyldopa, and cimetidine. Patients treated with chloramphenicol may respond poorly to this medicine. Serum levels of this medicine may be lowered by oral contraceptives. These interactions are unlikely to have clinical significance. Anti-metabolities and most antibiotics invalidate vitamins B12 assays by microbiological techniques.

Cyanocobalamin stimulates reticulocytes, thus playing important role in hematopoiesis in that, together with folic acid, it is involved in formation of deoxyribonucleotides from ribonucleotides.

Vitamin B12 is converted to Coenzyme B12 in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate.

Vitamin B12 is called an enzyme cofactor because it's required for certain enzymes to function. One of these enzymes, methionine synthase, produces an essential amino acid called methionine that helps add a chemical group called a methyl group to more than 100 different compounds, including DNA, RNA and proteins.

Vitamin B12 also activates another enzyme, LmethylmalonylcoA mutase, that produces a compound called succinylCoA, which is crucial for the citric acid cycle. As part of a complex series of biochemical reactions, the citric acid cycle uses dietary carbohydrates, fats and proteins to produce ATP, an essential energy source for all cells.

Cellular entry and exit of cobalamin (cbl) is a complex process. The story of cbl and its relation to anemia has been known for 50 years, but the slow unravelling of the complexities related to intracellular trafficking has been mainly due to a variety of reactions involved, complexity of cbl structure and the possible influence of structure on binding to intracellular proteins and hence on cellular entry and exit, and to the extremely low levels of tissue proteins which delayed their isolation.

A comparative study design was employed using 2 groups (Metformin and control) to identify how the cobalamin (vitamin B12) enter and traverse mammalian cells. A total of 21 patients with type 2 diabetes received sulfonylurea therapy; 14 of these 21 patients were switched to Metformin. Monthly serum total vitamin B12 measurements and holotranscobalamin (holoTCII) (B12-TCII) were performed. Patients receiving Metformin have diminished B12 absorption and low serum total vitamin B12 and TCII-B12 levels because of a calcium-dependent ileal membrane antagonism, an effect reversed with supplemental calcium.

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B12 suffered severe and swift optic atrophy.
Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B12.

Anaphylactic shock and death have been reported after parenteral vitamin B12 administration. No such reactions have been reported in clinical trials with Cyanocobalamin Tablets.

Persons taking most antibiotics, methotrexate or pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays. Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B12.

A study was conducted to compare the efficacy of sublingual and oral administration of 500 µg of cobalamin in subjects with cobalamin deficiency. Thirty subjects with low serum concentrations of cobalamin participated in the study. Subjects were randomly allocated to

receive one tablet daily of 500 µg cobalamin sublingually or orally, or two tablets daily of a vitamin B complex. It was concluded that no significant difference in concentrations between the treatment groups. A dose of 500 µg of cobalamin given either sublingually or orally is effective in correcting cobalamin deficiency.

Another study was conducted to identify effectiveness of oral versus intramuscular vitamin B12 to treat vitamin B12 deficiency. We conducted a systematic review searching databases for relevant RCTs. Outcomes included levels of serum vitamin B12, total serum homocysteine and methylmalonic acid, haemoglobin and signs and symptoms of vitamin B12 deficiency. The evidence derived from these limited studies suggests that 2000 mg doses of oral vitamin B12 daily and 1000 mg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term haematological and neurological responses in vitamin B12-deficient patients.
An intervention study in order to establish the efficacy of a supplement providing 500 µg Cyanocobalamin for four weeks in sixty-four institutionalized elderly residents, over 60 years of age, in Madrid (Spain). Before and after treatment, concentrations of serum cobalamin, serum holotranscobalamin, serum total homocysteine, and serum and red blood cell folate were analyzed. A supplementation with an oral supplement solution of 500 µg Cyanocobalamin daily for only four weeks, a shorter period than that found in former studies, may be considered suitable in institutionalized elderly.

A study was conduted to compare the efficacy and safety profile of a new proprietary oral vitamin B12 formulation (oral B12) with intramuscular (IM) vitamin B12 (IM B12) in restoring normal serum B12 concentrations in patients with low cobalamin levels (<350 pg/mL). Both the oral and IM formulations were effective in restoring normal levels of serum cobalamin in all patients studied (100%). Both formulations used in this study were well tolerated at the dose studied.

A study was conducted to assess the effect of supplementation with 1000g crystalline cobalamin, carried either by a milk product or a capsule, on cobalamin status in mildly cobalamin-deficient

elderly Dutch persons and it was concluded that crystalline cobalamin added to milk is an effective alternative to cobalamin capsules for improving cobalamin status.

This is a Phase 3, open-label, single-center, 8-week study was conducted to evaluating 50mcg daily intranasal Cyanocobalamin in patients previously maintained on monthly intramuscular B 12 injections. Treatment with CaloMist (Cyanocobalamin) nasal spray 50 mcg daily (one 25 mcg spray in each nostril) was effective at maintaining vitamin B 12 levels in patients with vitamin B 12 deficiency previously normalized on IM B 12 injections. No data is available to evaluate the efficacy of this B 12 preparation for the treatment of B 12 deficiency in patients previously untreated.

Cyanocobalamin has been marketed in the United States since 1942 and the safety of Cyanocobalamin is well established.

A study was conducted to the adverse event profile of the study drug in Study as well as the postmarketing adverse event reporting for both Cyanocobalamin products and OCEAN Premium Nasal Spray were evaluated in the safety review. The study concluded that no deaths during this 8 week study. There was one serious adverse event reported- a 51 year-old woman was diagnosed with inter vertebral disc protrusion on Day 52. She was treated with surgery and subsequently completed the study. There were no adverse events leading to withdrawal during this 8-week study. Overall, seventeen (68%) subjects reported at least one adverse event. The most common adverse events were nasopharyngitis, arthralgia, dizziness, headache, and rhinorrhea - each were reported by three (12%) subjects. Adverse events reported by two (8%) subjects included pain, bronchitis, pain in extremity, nasal discomfort, and rash. No new safety signals were noted in this small trial.

Cyanocobalamin Post marketing Reports identified several post marketing reports of angioedema and angioedema-like events occurring with Cyanocobalamin use.

There is no evidence from long-term use in patients with pernicious anemia that cyanocobalamin is carcinogenic. Pernicious anemia is associated with an 12increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with Cyanocobalamin.

During the initial treatment of patients with pernicious anemia, serum potassium must be observed closely the first 48 hours and potassium replaced if necessary.
IHematocrit, reticulocyte count, vitamin B12 , folate and iron levels should be obtained prior to treatment. Hematocrit and reticulocyte counts should be repeated daily from the fifth to seventh days of therapy and then frequently until the hematocrit is normal.

Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid and vitamin B12 diagnostic blood assays. Colchicine para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B12.

Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B 12 is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B12 that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for pregnant women (4 mcg daily) should be consumed during pregnancy.

Intake in children should be in the amount (0.5 to 3 mcg daily) recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

A study was conducted to evaluate the use of a combination of vitamins B1, B6, and B12 with dexamethasone in the treatment of the signs and symptoms of inflammatory neuropathy of the upper and lower limbs, in an open-label clinical trial. Patients were submitted to a 9-day treatment period with three doses of study medication at three day intervals, and a series of clinical and laboratory assessments, prior to the first dose of study medication and at each of the following three visits to the study center. Efficacy evaluations at each study visit included a

100mm VAS pain scale and global and satisfaction surveys completed by the patient and the investigating physician. Based on the results of this clinical study, we conclude that the combination of dexamethasone with the B-vitamins is safe and effective in the treatment of the signs and symptoms of inflammatory neuropathy.

A study was conducted to determine the efficacy and safety of the therapeutic combination of 10 mg piroxicam, 1 mg dexamethasone, 35 mg orphenadrine citrate, and 2.5 mg Cyanocobalamin (Rheumazin®) when compared with 20 mg piroxicam alone (Feldene®) in mandibular third molar surgery. There was no statistically significant difference in facial swelling between Rheumazin and Feldene (control group). Both drugs were equally effective in the control of pain, with Rheumazin displaying less adverse effects than Feldene. Therefore, Rheumazin appears to provide a better risk/ benefit ratio in the mandibular molar surgery. Since the side effects resulting from nonsteroidal anti-inflammatory drug administration are a severe limitation to the routine use of these drugs in clinical practice, our results suggest that Rheumazin can be a good choice for third molar removal treatment.

From the available safety profile of Cyanocobalamin 50 mcg Tablets, it is clearly evident that the side effects are known and there was one serious adverse effect & adverse event reported.

No new or unexpected safety concerns could arise from this application.





