REGISTRATION AND REGULATORY AFFAIRS DIRECTORATE

Summary of Product Characteristics (SmPC) Review Checklist

PRODUCT NAME: Fefodan-Z Capsules

section	Information required (please comment below, if requirements not fully met)	YES	NO
1.	{(Invented) name strength pharmaceutical form} 'FEFODAN-Z'Capsules: Dried Ferrous Sulphate 150 mg Zinc Sulphate monohydrate 61.8 mg Folic Acid 0.5 mg		
comment			
2.	**QUALITATIVE AND QUANTITATIVE COMPOSITION** Each Capsule contains: Pellets of Dried Ferrous Sulphate 150 mg (Equivalent to 45 mg of Elemental iron in timed-release form), Pellets of Zinc Sulphate monohydrate 61.8 mg USP (Equivalent to 22.5 mg of Elemental zinc in timed-release form) and Pellets of Folic Acid 0.5 mg Sustained release Capsules. For the full list of excipients see section 6.1.	.	
comment			
3.	**PHARMACEUTICAL FORM:** **CAPSULE:** White, yellow and brown coloured pellets filled in Hard gelatin capsule of size '0'. Transparent body printed with 'FEFODAN-Z' and orange colour cap printed with 'DANA' logo.		
comment			
4.	CLINICAL PARTICULARS: Iron & folate deficient megaloblastic anaemia**:** **4.2 Posology and method of administration**: Oral Prophylactic dose - one capsule daily. Therapeutic dose - one capsules 2-3 times daily. A liquid preparation maybe more appropriate for children. Children under 6 years or weighing less than 22kg; This medicine is not recommended. Elderly: The usual adult dose can be administered (see section 4.4). Method of administration: Oral administration. The capsules should not be sucked, chewed or kept in the mouth, but swallowed whole with water. Capsules should be taken before meals or during meals, depending on gastrointestinal tolerance. **4.3 Contraindications**: Hypersensitivity to any ingredients in the formulation; patients receiving repeated blood transfusions; concomitant parenteral iron; Patients with malignant disease, unless megaloblastic anaemia due to folic acid deficiency hemochromatosis and other iron overload syndromes. **4.4 Special warnings and precautions for use**:		

	Administer with caution in patients with haemolytic anaemia, haemoglobinopathies, iron storage or iron absorption diseases, existing gastrointestinal disease. The label will state 'Important warning: Contains iron. Keep out of the sight and reach of children, as overdose may be fatal'. This will appear on the front of the pack within a rectangle in which there is no other information. Patients with rare hereditary problems of galactose intolerance or fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product. Before starting treatment, it is important to exclude any underlying cause of the anaemia (e.g. gastric erosion, colonic carcinoma). Due to the risk of mouth ulcerations and tooth discolouration, tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with water. Aspiration of ferrous sulfate tablets can cause necrosis of the bronchial mucosa which may result in coughing, haemoptysis, bronchostenosis and/or pulmonary infection (even if aspiration happened days to months before these symptoms occurred). Elderly patients and patients who have difficulties swallowing should only be treated with iron sulfate tablets after a careful evaluation of the individual patient's risk of aspiration. Alternative formulations should be considered. Patients should seek medical attention in case of suspected aspiration. Folic acid should not be administered for treatment of pernicious anaemia or undiagnosed megaloblastic anaemia without sufficient amounts of cyanocobalamin (vitamin B_{12}) as folic acid alone will not prevent and may precipitate development of subacute combined degeneration of the spinal cord. Therefore a full clinical diagnosis should be made before initiating treatment. Folate should not be routinely used in patients receiving coronary stents. Caution should be exercised when administering folic acid to patients who may have folate dependent tumours. Folic acid is removed by haemodialysis. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. **4.5 Interaction with other medicinal products and other forms of interaction** Concurrent administration with tetracyclines may impair absorption		

	of both agents. The absorption of ciprofloxacin, norfloxacin and ofloxacin and bisphosphonates is reduced by oral iron. Cholestyramine may bind iron to the gastrointestinal tract, thus preventing its absorption. The absorption of iron salts is also decreased in the presence of antacids, preparations containing zinc, calcium, phosphorus, trientine, or when taken with tea, coffee, milk, eggs and whole grains. Iron supplements should not be taken within one hour before or two hours after ingestion of these products. Iron salts may reduce the bioavailability of methyldopa. The absorption of levodopa and penicillamine may be reduced. Absorption of iron salts is enhanced by ascorbic acid and meat. Dimercaprol: Avoid the concomitant use of iron with dimercaprol. Thyroid hormones: Oral iron reduces the absorption of levothyroxine (thyroxine) thus should be given at least 2 hours apart. Absorption of folic acid may be reduced by sulfasalazine. Concurrent administration with cholestyramine may interfere with folic acid absorption. Patients on prolonged cholestyramine therapy should take folic acid 1 hour before or 4 to 6 hours after receiving cholestyramine. Antibiotics may interfere with the microbiological assay for serum and erythrocyte folic acid concentrations and may cause falsely low results. Trimethoprim or sulfonamides, alone or in combination as co-trimoxazole, may reduce the effect of folic acid and this may be serious in patients with megaloblastic anaemia. Serum levels of anticonvulsant drugs (phenytoin, phenobarbital, primidone) may be reduced by administration of folate and therefore patients should be carefully monitored by the physician and the anticonvulsant drug dose adjusted as necessary. Fluorouracil toxicity may occur in patients taking folic acid and this combination should be avoided. Edible clay or antacids containing aluminium or magnesium may reduce folic acid absorption. Patients should be advised to take antacids at least two hours after administration of folic acid. Folic acid may reduce intestinal absorption of zinc (of particular importance in pregnancy). When taken together, zinc may reduce the absorption of tetracyclines (but not doxycycline), and quinolone antibiotics. In addition, zinc may also interfere with the absorption of cephalexin or ceftibuten. An interval of at least three hour should be allowed between administration of zinc and any of these medicines. **4.6 Pregnancy and Lactation:** Ferrous salts are recommended for use in pregnancy and lactation,		

and no contraindications to such are known.

Folic acid deficiency during pregnancy may lead to the appearance of foetal malformations. Imbalance in folate requiring trophoblast cells may also lead to detachment of the placenta.

Very high doses of folic acid have been shown to cause foetal abnormalities in rats; however, harmful effects in the human foetus, mother or the pregnancy have not been reported following ingestion of folic acid.

Breastfeeding

Folic acid is excreted in breast milk.

No adverse effects have been observed in breast-fed infants whose mothers were receiving folic acid.

Zinc crosses the placenta and is present in breast milk. The safety of Fefodan-Z capsules in lactation has not been established.

4.7 Undesirable effects:
There is no evidence regarding the effect of zinc on the ability to drive or use machines, although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce gastrointestinal side-effects.

Large doses may produce gastro-intestinal irritation, nausea, vomiting, epigastric pain, diarrhoea.

Constipation may be caused by continual administration, particularly in older patients, and may lead to faecal impaction.

Iron supplementation may cause the blackening of stool.

Hypersensitivity reactions have been reported. These range from rashes, sometimes severe, to anaphylaxis.

Bronchial stenosis (see section 4.4)

<u>Reporting of suspected adverse reactions:</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

Post-marketing: The following ADRs have been reported during post-marketing surveillance. The frequency of these reactions is considered not known (cannot be estimated from the available data).

Gastrointestinal disorders:

mouth ulceration*

* in the context of incorrect administration, when the tablets are

chewed, sucked or kept in mouth. Elderly patients and patients with deglutition disorders may also be at risk of oesophageal lesions or of bronchial necrosis, in case of false route. Folic acid is generally well tolerated although the following side effects have been reported:

Blood and lymphatic system disorders:

Folic acid may worsen the symptoms of co-existing vitamin B_{12} deficiency and should never be used to treat anaemia without a full investigation of the cause.

Immune system disorders:

Rare: Allergic reactions, comprising erythema, rash, pruritus, urticarial, dyspnoea, and anaphylactic reactions (including shock).

Gastrointestinal disorder:

Abdominal distension, flatulence, anorexia and nausea.

4.8 Overdose:

Acute iron overdosage can be divided into four stages. In the first phase, which occurs up to 6 hours after oral ingestion, gastrointestinal toxicity, notably vomiting and diarrhoea, predominates. Other effects may include cardiovascular disorders such as hypotension and tachycardia, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally pass this first phase. The second phase may occur at 6-24 hours after ingestion and is characterised by a temporary remission or clinical stabilisation. In the third phase gastrointestinal toxicity recurs together with shock, metabolic acidosis, convulsions, coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and pulmonary oedema. The fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Overdosage of ferrous salts is particularly dangerous to young children.

Treatment consists of gastric lavage followed by the introduction of 5g desferrioxamine into the stomach. Serum iron levels should be monitored and in severe cases iv desferrioxamine should be given together with supportive and symptomatic measures as required. Gastric lavage with 5% sodium bicarbonate and saline cathartics (*e.g.* sodium sulfate 30g for adults); milk and eggs with 5g bismuth carbonate every hour as demulcents. Blood or plasma transfusion for shock, oxygen for respiratory embarrassment. Chelating agents (*e.g.* disodium calcium edetate) may be tried (500mg/500ml by continuous iv infusion). Dimercaprol should not be used since it forms a toxic complex with iron. Desferrioxamine is a specific iron chelating agent and severe acute poisoning in infants should always

	be treated with desferrioxamine at a dose of 90mg/kg im followed by 15mg/kg per hour iv until the serum iron is within the plasma binding capacity. For Folic acid, No cases of acute overdosage appear to have been reported, but even extremely high doses are unlikely to cause harm to patients. No special procedures or antidote are likely to be needed. High doses of zinc cause emesis. In addition, zinc sulfate is corrosive at high doses, and may cause irritation and corrosion of the gastrointestinal tract, including ulceration of the stomach and possible perforation. Over dosage with zinc has also been associated with acute renal tubular necrosis and interstitial nephritis. Prolonged high dose zinc supplementation may result in copper deficiency.		
comment			
5.	***5.2* Pharmacokinetics properties:** **5.1 Pharmacodynamics properties** ATC CODE: B03A A07 Ferrous sulfate is used in the treatment of iron deficiency anaemias. Iron preparations have no intrinsic therapeutic activity except as a nutrient source: their use without evidence of iron deficiency, or reasonable expectation of its occurrence, is to be deprecated. Excessive iron is toxic and haemochromatosis can result from chronic injection of iron preparations used as tonics, especially in individuals with undiagnosed blood disorders. Patients with chronic anaemia are particularly at risk from iron storage disease. Recently a severe iron overload myopathy has been described in patients given prophylactic iron indiscriminately while receiving haemodialysis. Genetic factors probably contribute to the risk of an iron storage disease. It should be clear that although iron deficiency is easily treated, its detection does not constitute a complete diagnosis. Every effort should be made to determine why the patient has a state of negative iron balance. Attention should be given to hidden sources of haemorrhage (which may indicate serious urinary or gastrointestinal conditions) and also the possibility of malabsorption of iron caused by latent disease of the small intestine. The mucosa of the duodenum and upper part of the jejunum are rich in dihydrofolate reductase, where folates and folic acid are absorbed. Once absorbed, folic acid is rapidly reduced and then methylated to form tetrahydrofolic acid derivatives which are rapidly transported to the tissues. Pharmacotherapeutic group: Other mineral supplements, ATC code: A12CB01		

	5.2 Pharmacokinetics properties Folic acid is readily absorbed following oral dosage, and is extensively bound to plasma proteins, Iron is irregularly and incompletely absorbed from the gastrointestinal tract, the main sites of absorption being the duodenum and the jejunum. Absorption is aided by the acid secretion of the stomach or by dietary acids and is more readily affected when the iron is in the ferrous state or is part of the haem complex (haem-iron unit). Absorption is also increased in conditions of iron deficiency or in the fasting state but decreased if the body stores are overloaded. Around 5-15% of the iron ingested in food is absorbed. **Following absorption,** the majority of iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin. The remainder is stored within ferritin or haemosiderin or is incorporated into myoglobin with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin. Only very small amounts are excreted as the body reabsorbs the iron after the haemoglobin has broken down. **5.3 Preclinical safety data:** Toxicity studies in animals (rats and rabbits) have shown that massive doses (100mg/kg upwards) produce precipitation of folate crystals in renal tubules, particularly proximal tubules and ascending limb of the loop of Henle. Tubular necrosis is followed by recovery. Non-clinical data have not revealed significant hazards for human, based on standard studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity. Effects in non-clinical studies were observed only at exposures sufficiently in excess of the maximum human exposure to be of little clinical relevance. Non stated for zinc sulphate and ferrous sulphate.		
Comment			
6.	6.1 **List of excipients:** Non Pareil Seeds (Dummy) EHG Capsules Size '0' Clear transparent coloured Body printed "FEFODAN-Z" and Orange coloured Cap printed "DANA" logo. **6.2 Incompatibilities:** None known. **6.3 Shelf life:** 3 years from the manufacturing date. **6.4 Special precautions for storage:** Store below 30^0C, store in a cool, dry place away from sunlight		

	Keep from the reach of children. **6.5 Nature and contents of container <and special equipment for use, administration or implantation:** The pellets are packed in hard gelatin capsule shells of 2 Blisters of 15 capsules packed in printed Mono-carton. The blisters are made up of printed PVC aluminium foil. **6.6 Special precautions for disposal:** Not applicable.		
Comment			
7.	**Marketing authorization holder** Dana Pharmaceuticals Ltd. Shiroro Dam Road, Maitumbi, Minna. Niger State. Nigeria.		
8.	**Marketing authorization number(s)** A4-2955		
9.	**Comments on deficiencies with reference to table above and specific sections of the SmPC**		
10.	**Additional data requested (to be communicated to the applicant)**		

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