1. NAME OF THE MEDICINAL PRODUCT

JAWARON TONIC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains:

Raw Materials	
Ferrous Gluconate	120mg
Vitamin B1(Thiamine HCL)	1.0mg
Vitamin B2(Riboflavin)	1.0mg
Vitamin B6(Pyridoxine)	2.0mg
Vitamin B12	1mcg
Nicotinamide	5mg
Zinc Sulphate	15mg
Lysine Hydrochloride	100mg

3. PHARMACEUTICAL FORM

Oral Syrup

4. CLINICAL PARTICULARS

Therapeutic indications

In iron – deficiency anaemias (prophylaxis and therapy), in pregnancy, lactation, anorexia, malaria fever and other febrile illnesses, for general improvement of health and maintenance of normal body metabolism in sportsmen, old people, students and convalescing patients. It is also indicated during menstruation and puberty. It is also indicated in antibiotic therapy, and could be used as a comprehensive vitamins and iron supplement after surgery.

Posology and method of administration

CHILDREN: 6 – 12 years; one teaspoonful (5ml) twice daily.
ADULTS: 2 teaspoonfuls (10ml) twice daily or as directed by physician
CHILDREN LESS THAN 6 YEARS OLD: As directed by the physician.
(2mg of iron per kg body weight 3 times daily)

Special warnings and precautions for use

Iron absorption is maximum in empty stomach. So, it is advisable that JAWARON Tonic be taken in-between meals.

Interaction with other medicinal products and other forms of interaction

Contraindications:

1. Primary (Idiopathic) or secondary iron storage.
2. Anaemias associated with ineffective erythropoiesis, marrow hypoplasia, sideroblastic change, uncompleted vitamin B_{12} or foliate deficiency.
3. Oral iron may aggravate severe acute inflammatory intestinal disease and is ineffective in patients with extensive small intestine disease.
4. In patients with known idiosyncrasy to commonly used ingredients and excipients, oral iron preparations should not be administered.
5. Iron compounds should not be given to patients receiving repeated blood transfusion.
6. Oral iron therapy should not be administered concomitantly with parenteral iron.

Fertility, Pregnancy and lactation

Pregnancy

No teratogenic effect

Effects on ability to drive and use machines

None

Undesirable effects

Jawaron Tonic is well tolerated and doesn't cause any significant side effects. However therapeutic does of iron may cause gastro intestinal discomfort, diarrhea and vomiting in some individuals. These side effects, when they occur, are related to the amount of elemental iron rather than the type of preparation. Although iron is better absorbed between meals, side effects can be reduced by taking it with milk or immediately after food. Continued, chronic, administration may cause constipation and the excretion of excess iron through faeces may lead to the passage of dark stools. Oral iron liquid preparations may blacken the teeth.

Overdose

In treating acute iron poisoning, speed is essential to block absorption of iron from the alimentary tract. Emesis or lavage should be considered and serum iron concentrations may be an aid to estimating the severity of poisoning. Chelation therapy with desferrioxamine may be necessary. Saline cathartic is advised after the stomach contents are washed out with % sodium bicarbonate solution. Daily intravenous infusion of desferrioxamine 6-12g over 12 hours may be used. It can also be given by intramuscular injections.

Other measures include the symptomatic management and therapy of metabolic and cardiovascular disorders.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS

Pharmacotherapeutic group:

Hematinic

Mechanism of action:

Following absorption, the majority of the iron is bound to transferring and transported to the bone marrow where it is incorporated into haemoglobin, the remainder is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferring. Only small amounts of iron are excreted as the majority released after the destruction of the haemoglobin molecule is reused. This conservation of body iron and lack of an excretory mechanism for excess iron, is the reason for the development of iron overload with excessive therapy or repeated transfusions. (Harju E. CLin. Pharma Cokinet 1989, 17: 69-89).

The usual therapeutic dose of iron is about 200mg per day (2 to 3mg / kg). In selecting the optimal dose for adults allowance should be made for body size. Children weighing 15 to 30kg can take half the average adult dose and smaller children and infants can tolerate relatively larger does of iron for example 5mg/kg. The dose employed is a practical compromise between the therapeutic action desired and the toxic effects. It is the physicians responsibility to modify dosage to meet the needs of the individual patients. Prophylaxis and mild nutritional iron deficiency may be managed with modest does. When the object is the prevention of iron deficiency in pregnant patients, for example, does of 15 to 30mg of iron per day, if not taken with meals, are adequate to meet the 3 – to – 6 – mg daily requirement of the last two trimesters. When the purpose is to treat iron-deficiency anaemia, but the circumstances do not demand haste, a total of

about 100mg (35mg, three times daily) may be used. The average dose for the treatment of iron-deficiency. Anaemia is about 200mg of iron per day, given in three equal does of 65mg. in the case of continued bleeding, as much as 120mg may be administered four times daily. The usual therapeutic does of iron results in an increase of between 0.15 and 0.25g of haemoglobin per deciliter of whole blood per day, beginning on the third or fourth day of treatment. An estimate of the effects to be expected from different amounts of oral iron are given in the table below:

AVERAGE RESPONSE TO ORAL IRON

Total Dose mg of Iron per day	Estimated Iron Absorption		Increase in Haemoglobin g/dl of blood per day
	%	mg	
35	40	14	0.07
105	24	14	0.14
195	18	35	0.19
380	12	45	0.22

The above effects may be modified by the severity of the iron-deficiency anaemia and by the time of ingestion of iron relative to meals. It is well established that amount of iron absorbed increases progressively with larger does; however, the percentage absorbed decreases and the therapeutic value of larger does is offset by an increase in the frequency of undesirable gastro-intestinal symptoms. (Clement A. Pharmacological Basis of Therapeutics 6th Edition 1980

1322 – 1324)

The duration of treatment is governed by the recovery of haemoglobin and the desire to create iron stores (Norby A, J. Lab. Clin. Med. 1976, 87, 670 – 679). The former depends on the severity of the anaemia with a daily rate of repair of 0.2g of haemoglobin per deciliter of whole blood, the red-cell mass is usually reconstituted within 1 to 2 months. Thus the individual with 5g of haemoglobin per deciliter may achiever a normal complement of 15g per deciliter in about 50 days, whereas the individual with a haemoglobin of 10g per deciliter may take only half that time.

The creation of stores of iron is a different matter, requiring many months of oral iron administration. The rate of absorption decreases rapidly after recovery from anaemia and after 3 to 4 months of treatment, stores may be increasing at a rate of not much more than 100mg per month. Much of the strategy of continued therapy depends on the estimated future iron balance of the individual. The person with an inadequate diet may require continued therapy with low does of iron. The individual whose bleeding has stopped will require no further therapy after the haemoglobin has returned to normal. For the individual with continued bleeding, chronic therapy is clearly indicated.

5.2 Pharmacokinetic properties

Distribution

While the iron content of the diet is obviously important of greater nutritional significance is the bioavailability of iron in food (Cook and Finch; Blood 1976, 48, 449-455). Iron is irregularly and incompletely absorbed from the gastro-intestinal tract, the main sites of absorption being the duodenum and Jejunum. Absorption is aided by the acid secretion of the stomach or by dietary acids (Such as ascorbic acid) and is more readily affected when the iron is in the ferrous state or is part of the haemcomplex (Haem-Iron). Of the two forms of iron that are absorbed, this haem iron is by far more available and its absorption is independent of the composition of the diet.

Its relative absorption is illustrated by the study carried out by Bjorn-Rasmussen (Bjorn-Rasmussen and Castle, J. Clin. Invest. 1974,53,247-255) In which a diet was fed that contained 17.4mg of iron per day, of which 16.4mg was none haem and 1mg was contained in haem; 37%, of the haem iron but only 5% of the non haem iron was absorbed. Nevertheless, it is the bioavailability of the non haem fraction that deserves the greatest attention, since it represents by far the largest amount of dietary iron and is almost exclusively the form of dietary iron that is ingested by the economically under privileged. Unfortunately, non haem iron is usually unavailable and its absorption is profoundly affected by other foods ingested concurrently in a vegetarian diet, non haem iron is absorbed very poorly because of the inhibitory action of a variety of components, particularly phosphates. Two substances are known to facilitate the absorption of non haem iron; ascorbic acid and meat. Ascorbate forms complexes with and or reduces ferric to ferrous iron. While meat facilitates the absorption of iron by stimulating production of gastic acid, it is possible that some other effect not yet identified is also involved. Either of these substances can increase bioavailability several fold. Thus assessments of bioavailable dietary iron should include not only the amount of iron ingested but also an estimate of its bioavailability based on the intake of substances that enhance its absorption. The effect of iron status on the absorption of non haem iron in food can be illustrated with the following graph:-

Availability of Non Haem Iron

The percentage of iron absorbed from diets of low,medium and high bioavailability in individuals with iron stires of 0, 250, 500 and 1000mg are portrayed (Mosen and Hallberg, AM.J.Clin. Nutr 1978, 31, 134-141)

Obviously, pregnancy and infancy represent periods of negative balance. The menstruating woman is also at risk whereas iron balance in the adult male and non-menstruating reasonably secure. The difference between dietary supply and requirements is reflected in the size of iron stores. These will be low or absent when iron balance is precarious and high when iron balance is favorable. Thus, in the infant after the third month of life and in the pregnant woman after the first trimester, stores of iron are negligible. Menstruating females have approximately one third the stored iron found in the adult male, indicative of the extent to which the additional average daily loss of 0.5mg of iron affects balance. The daily iron intake and absorption can be summarized in the following table:

Subject	A	B	C	D	E	F	G
Infant	8	100	67	3	33	66	0.5
Child	20	80	22	9.6	48	96	2
Adolescent(Male)	60	50	21	18	30	60	1.5
Adolescent(Female)	50	50	20	15	30	60	1.5
Adult (Male)	70	40	13	18	26	52	2
Adult (Female)	60	30	21	11	18	36	1
Pregnant (Female)	60	30	73	11	18	36	0.25

Where: A: Weight (kg), B: Calories (Intake/kg) C: Iron requirement(mg/kg)
D: Total dietary iron (mg), E: Available iron in poor diet (mg/kg)
F: Available iron in good diet (mg/kg)
G: Safety factor (Available iron/requirement)

Food iron content is based on the ratio of 6mg of iron per 1000kcal.Low bioavailability of dietary iron is considered to permit 10% and high bioavailability 20% absorption in the iron deficient subject. The basal requirement (that for the adult male) is assumed to be 13mg/kg while that of menstruation: 5mg/kg. Requirement for growth is based on 35mg of iron for each gram-increase in weight. Thus 5mg/kg per day in infancy reflects a weight gain of 15g per day, equivalent to 430mg of iron divided by 8kg of body weight. To this was added the 13mg/kg basal iron requirement

Similarly, calculation of growth requirements in children and in the adolescent male and female were based on a weight increase of 5,15 and 10g per day, respectively, corresponding to iron requirement of 9,9 and 7mg/kg per day. In pregnancy, requirements for the second and third trimester have been estimated at 3 to 5mg per day. Safety factor is calculated for a dietary iron absorption of 10% (Clement A, Pharmacological basis of therapeutics 6th edition 1980.1318-1320).

On the other hand the other entire active ingredients in Jawaron tonic have good bio availabilities. Small amounts of Thiamine are well absorbed from the gastro-intestinal tract following oral administration, but the absorption of doses larger than about 5mg is limited. Riboflavin is also well absorbed from the G.I.T. Pyridoxine, Pyridoxal and Pyridoxamine are also readily absorbed from the G.I.T.

Vit B12 (Cyanocobalamin) substances bind intrinsic factor, a Glycoprotein secreted by the gastric mucosa and are then activity absorbed from the gastro-intestinal tract (G.I.T). Absorption is impaired in patients with absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut or after gastrectomy. Absorption from the G.I.T can also occur by passive diffusion. Little of the vitamin present in diets is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically.

Nicotinamide is also very readily absorbed from the gastric intestinal tract.

The Body store of iron is divided between iron-containing compounds that are essential and those in which excess iron is held in storage. From a quantitative standpoint, haemoglobin dominates the essential fraction. This protein with a molecular weight of 64,500, contains four atoms of iron per molecule amounting to 1.1mg of iron per milliliter of red blood cells. Other forms of essential iron include myoglobin and a variety of haem and non-haem iron-dependent enzymes. Ferritin is the protein of iron storage, and it exists as individual molecules or in an aggregated form. Apoferitin has a molecular weight of about 450,000 and is composed of some 24 polypeptide sub-units; these form an outer shell within which there is a storage cavity for polynuclear hydrous ferric oxide phosphate (Harrison. p.m. Semin. Haematol, 1977, 14,55-70). Over 30% of the weight of ferritin may be iron. Aggregated ferritin referred to as haemosiderin and visible
by light microscopy constitutes about one third of normal stores, a fraction that increases as stores enlarge. The two predominant sites of iron storage are the reticuloendothelial system and the hepatocytes, although some storage also occurs in muscle. Internal exchange of iron is accomplished by the plasma protein transferring (Aisen P and Brown E., Semin, Haematol, 1977, 14, 31, -53).

This β_1-Glycoprotein has a molecular weight of about 76,000 and two binding sites for ferric iron. Iron is delivered from transferring to specific receptors on tissue cell membrances. The concentration of these receptors for transferring on a given cell is related to the widely disparate requirement of different tissues for iron. The essential role of transferrin is illustrated by the maldistribution of iron that occurs in congenital atransferrinaemia. These patients have iron-deficiency anaemia despite excessive concentrations of iron in nonerythroid tissues (Goya N. et al. Blood, 1972 40, 239 – 245)

The flow of iron through the plasma amounts to a total of 30 to 40 mg per day in the adult (About 0.46mg/kg of body weight). The major internal circulation of iron involves the erythron and the reticuloendothelial cell. About 80% of the iron in plasma goes to the erythroid marrow to be packaged into new erythrocytes; these normally circulate for about 120 days before being catabolized by the reticuloendothelium, at that time a portion of the iron is immediately returned to the plasma bound to transferring, while another portion is incorporated into the ferritin stores of the reticuloendothelial cell and is returned to the circulation more gradually Isotopic studies indicate some degree of iron wastage in this process wherein defective cells or unused portions of their iron are transferred to the reticuloendothelial cell during maturation, by passing the circulating blood in haemolytic anaemia. The update of iron by the erythron may increase by as much as eight fold, with a corresponding increase in red-cell breakdown. When there are abnormalities in maturation of red, cells, the predominant portion of iron assimilated by the erythroid marrow may be rapidly localized in the reticuloendothelial cell as defective red cell precursors are broken down; this is termed ineffective erythropoiesis. With red cell aplasia the rate of turnover of iron in plasma may be reduced by one half or more, with

all of the iron now going to the hepatocyte for storage. It should be noted that non-erythroid tissues do not have the ability of the erythron to increase their number of membrane receptors for transferring; their capacity to take up iron is thus always limited.

Elimination
The most remarkable feature of iron metabolism in man is the degree to which the body store is conserved. Only 10% of the total is lost per year from normal men, that is, about 1mg per day (Green .R. et al Am .J. Med. 1968, 45, 336-353). Two thirds of this iron is excreted from the gastro-intestinal tract as extravasated red cells, iron in bile, and iron in exfoliated mucosal cells. The other third is accounted for by small amounts of iron in desquamated skin and in the urine. Physiological losses of iron in the male vary over a relatively narrow range, decreasing to about 0.5mg in the iron deficient individual and increasing to as much as 1.5 or possibly 2mg per day when excessive iron is consumed. Additional losses of iron occur in the female due to menstruation (Hallberg. L. et al Acta Med. Scand 1966c, 181 Suppl. 459, 11-21)

While this averages about 0.5mg per day, 10% of normal menstruating females lose over 2mg per day. Menstrual losses are influenced by various types of contraceptive therapy, loss is reduced by about one half when estrogen-containing oral contraceptives are used and is increased by intrauterine devices. Pregnancy imposes a requirement for iron of even greater magnitude. In addition to this physiological loss, there is a great variety of other causes of iron loss. Examples include the donation of blood, the use of anti-inflammatory drugs; they cause bleeding from the gastric mucosa, gastro-intestinal disease with associated bleeding and so forth. Much rarer is the haemosiderinuria that follows intravascular haemolysis which may result in urinary losses of iron of as much as 20mg per day; still rarer is pulmonary siderosis, wherein iron is deposited in the lungs and becomes unavailable to the rest of the body.
When red blood cells have lived their life span and are destroyed, the haemoglobin released from the cells is ingested by the cells of the macrophage-monocyte system. There, free iron is liberated, and it can then either be stored in the ferritin pool or be resued for formation of haemoglobin.

About 1mg of iron is excreted each day by men, mainly into the faeces. Additional quantities of iron are lost whenever bleeding occurs. Thus, in women the menstrual loss of blood brings the average iron loss to a value of approximately 2mg per day. Obviously, the average quantity of iron derived from the diet each day must at least equal that lost from the body (Guyton A.C. Textbook of Medical Physiology 7th edition, 1986, 47)

5.3 Preclinical safety data
Not applicable

6.0 PHARMACEUTICAL PARTICULARS
List of excipients

Methylparaben
Propylparaben
Bronopol
Dextrose Monohydrate
Sorbitol 70% Solution
Citric Acid
Propylene Glycol
Sodium Citrate
Allura Red
Disodium EDTA
Malt Flavour
Orange Sweet Conc.
Essence Sweet Orange
Sugar

Incompatibilities

None

Shelf life

2 years

Special precautions for storage

Store in cool & dry place, below 30°C. Protect from Light.

Nature and contents of container
It is presented in amber coloured 200ml and 100ml glass bottles with pilfer – proofed caps.

7.0 MARKETING AUTHORISATION HOLDER

JAWA INTERNATIONAL LIMITED
Jawa House Compound, Plot 6 Abimbola Way,
Isolo Industrial Estate, Isolo,
Lagos, Nigeria
Phone: +2348073894283. E-mail: contactus@jawasil.com

8.0 MANUFACTURED BY:

JAWA INTERNATIONAL LIMITED
Jawa House Compound, Plot 6 Abimbola Way,
Isolo Industrial Estate, Isolo,
Lagos, Nigeria
Phone: +2348073894283. E-mail: contactus@jawasil.com