SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TOTYLEM 60 mg/0.4 mg, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Iron (as ferrous gluconate hydrate) ....60.000 mg

Folic acid (as folic acid hydrate) ....0.400 mg

For one film-coated tablet.

Excipient with known effect: each film-coated tablet contains 158 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pearly pink, round film-coated tablet of 12 mm diameter and 7 mm thickness.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Prophylaxis and treatment of iron deficiency with increased need for folic acid during pregnancy, postpartum and breastfeeding.

4.2. Posology and Route of Adminstration

Posology

1 tablet daily (60 mg iron and 0.4 mg folic acid).

Duration of the treatment

In case of prophylactic treatment, pregnant women should be treated for 6 months, or, if 6 months of treatment cannot be achieved during the pregnancy, continue the prophylaxis during postpartum period (6 to 12 weeks after childbirth).

In case of iron deficiency, duration of use should be long enough to restore the iron stores (serum iron, serum transferrin receptor and transferrin saturation coefficient).

Serum hemoglobin and ferritin levels should be checked 8 weeks after treatment initiation. The need of any subsequent monitoring is left to the discretion of the physician. In pregnant women, these tests should be repeated at least once during the second trimester.

Children and adolescents

The product is not intended for use in the pediatric population as only indicated in women during pregnancy, postpartum and breastfeeding.

Elderly patients

The product is not intended for use in the elderly population as only indicated in women during pregnancy, postpartum and breastfeeding.

Patients with renal impairment

No dosage adjustment is generally necessary in patients with renal impairment (see section 4.4). Nevertheless, in case of severe renal impairment, iron should be administered intravenously.

Patients with hepatic impairment

No dosage adjustment is generally necessary in patients with hepatic impairment (see section 4.4).

Method of administration

Oral use.

The tablets should not be sucked, chewed or kept in the mouth, but swallowed whole with a glass of water (see section 4.4). Tablets should be taken before meals or during meals, depending on gastrointestinal tolerance, taking into account possible interactions with certain foods (see section 4.5).

4.3. Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Iron overload such as hemosiderosis or haemochromatosis, normo- or hypersideraemic anaemia such as thalassemia, refractory anaemia, aplastic anaemia.

Non-iron deficiency anaemias (such as haemolytic anaemia, vitamin B12-deficiency megaloblastic anaemia).

Repeated or chronic blood transfusions.

4.4. Special warnings and precautions for use

Iron supplementation has no effect on abnormally low iron blood concentrations related to inflammatory syndromes.

Iron supplementation should, as far as possible, be combined with treatment of the cause.

Patients with existing gastrointestinal diseases such as chronic inflammatory bowel diseases, bowel stenoses, diverticula, gastritis, gastric and intestinal ulcers should be treated carefully with TOTYLEM.

The metabolism of folic acid and the metabolism of vitamin B12 are intimately linked such that deficiency of either vitamin leads to megaloblastic anaemia and/or overlapping neurologic manifestations. The administration of folic acid in the presence of vitamin B12 deficiency does not prevent the appearance of clinical signs and may lead to both neurologic and, later, hematologic relapse. A Vitamin B12 deficiency therefore needs to be excluded before treatment with TOTYLEM.

In patients with clinically relevant folic acid deficiency a preparation with higher amounts of folic acid is needed.

Patients with deglutition disorders may be at risk of pharyngeal ulceration, oesophageal lesions.

Aspiration of iron 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). Patients who have difficulties swallowing should only be treated with iron 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 (see Section 4.8).

Due to the risk of tooth staining and ulceration of the mouth, throat and oesophagus, tablets should not be sucked, chewed or kept in the mouth but swallowed whole with a large glass of water.

This medicinal product may change stool colour (black) without clinical consequences.

According to data published in the literature, the lining of the stomach and gastrointestinal tract of patients receiving iron-based treatments may be pigmented, which may interfere with gastrointestinal surgery (see section 4.8).

Patients with liver dysfunction including alcoholic liver disease, non-alcoholic fatty liver disease, and viral hepatitis should be carefully treated with TOTYLEM.

Patient with renal impairment may have an increase of their iron requirement. Patients with severe and chronic kidney disease who need erythropoietin should be treated with caution and iron should be administered intravenously since oral administered iron is poorly absorbed in uremic individuals (see section 4.2).

Concomitant intake of large quantities of tea or coffee inhibits the absorption of iron (see section 4.5). Accidental high intake can lead to serious intoxication, especially in small children (see section 4.9).

<u>Related to excipients:</u>

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium- free'.

4.5. Interactions with other medicinal products and other forms of interaction

Effects of other medicinal products on TOTYLEM

<u>Unrecommended combinations</u>

Iron (salts of) (by injection)

Lipothymia or even shock due to the rapid release of iron from its complex form and transferrin saturation.

<u>Combinations requiring precautions for use</u>

Calcium

Decreased gastrointestinal absorption of iron salts.

Iron salts should be taken between meals and not with calcium.

Cholestyramine

Decreased gastrointestinal absorption of iron salts.

Iron salts should be taken within 1 to 2 hours before or 4 hours after ingestion of cholestyramine.

Antacids (incl. aluminium, calcium and magnesium salts), proton pump inhibitors

and adsorbants
Decreased gastrointestinal absorption of iron salts.
Administration of iron salts with antacids and adsorbants should be separated by more than 2 hours (if possible).

Trientine
Decreased gastrointestinal absorption of iron salts.
Administration of iron salts with trientine should be separated (by more than 2 hours if possible).

Food products
Phytic acids (whole grains), vegetables, polyphenols (tea, coffee, red wine), calcium (milk, dairy products) and some proteins (eggs) significantly impair the absorption of iron.
Administration of iron salts should be separated from these foods by more than 2 hours (if possible).

Combinations to be taken into account
Folic acid antagonists
Folic acid antagonists such as methotrexate or sulfasalazine may decrease the effect of folic acid because of their antagonistic properties.

Chloramphenicol
Simultaneous administration of chloramphenicol and folic acid may distort the hematopoietic response to folic acid.

5-fluorouracil and other oral fluoropyrimidines
Both the cytostatic and undesirable effects of 5-fluorouracil and other oral fluoropyrimidines may be potentiated by concomitant administration of high doses of folic acid.

Effects of TOTYLEM on other medicinal products.

Combinations requiring precautions for use
Bisphosphonates (oral route)
Decreased gastrointestinal absorption of bisphosphonates.
Administration of iron salts should be separated from that of bisphosphonates (by at least 30 minutes to more than 2 hours, if possible, depending on the bisphosphonate).

Tetracyclines (oral route)
Decreased gastrointestinal absorption of cycline antibiotics (formation of complexes).
Administration of iron salts with cycline antibiotics should be separated by more than 2 hours (if possible).

Entacapone
Decreased gastrointestinal absorption of entacapone and iron due to chelation of iron by entacapone. Administration of iron salts with entacapone should be separated by more than 2 hours (if possible).

Fluoroquinolones, thyroid hormones, carbidopa, levodopa, methyldopa, penicillamine, strontium, zinc
Decreased gastrointestinal absorption of these substances.
Administration of iron salts with these substances should be separated by more than 2 hours (if possible).

HIV integrase inhibitors
Decreased gastrointestinal absorption of HIV integrase inhibitors in case of concomitant use under fasted conditions.

Iron salts should be taken with HIV integrase inhibitors either separately (by more than 2 hours if possible) or together with food

Phenobarbital, primidone, phenytoin, fosphenytoin, carbamazepine, pheneturide
Plasma concentrations of these anticonvulsants are decreased by an increase in their metabolism of which folate is one of the co-factors.
Clinical monitoring, control of plasma concentrations of the antiepileptic drug and dose adjustment, if appropriate, is required during folic acid supplementation and after its discontinuation.

Combination to be taken into account
Acetohydroxamic acid
Decreased gastrointestinal absorption of the two medicinal products by iron chelation.

4.6. Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicates no malformative nor feto/neonatal toxicity. TOTYLEM can be used during pregnancy if clinically needed.

Breastfeeding

Iron and folic acid are excreted in human milk but at therapeutic doses of TOTYLEM no effects on the breastfed newborns/infants are anticipated. TOTYLEM can be used during breast-feeding.

Fertility

No sufficient data regarding the effects of ferrous gluconate and folic acid on fertility are available.

4.7. Effects on ability to drive and use machines

No study has been conducted with TOTYLEM to assess the effects on ability to drive and use machines. It is anticipated that TOTYLEM has no or a negligible effect on the ability to drive and use machines.

4.8. Undesirable effects

Undesirable effects are listed according to the MedDRA system organ classification and are cited below as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Common	Frequency not known (cannot be estimated from the available data)
Immune system disorders		Hypersensitivity, anaphylactic reaction
Respiratory, thoracic and mediastinal disorders		Bronchial stenosis, pulmonary necrosis (see section 4.4)
Gastrointestinal disorders	Constipation, diarrhoea, abdominal distension, abdominal pain, nausea, heartburn, vomiting, black stools (usual colour).	Stained teeth*, gastrointestinal irritation, gastritis, gastrointestinal pseudomelanosis**, mouth ulceration, pharyngeal ulceration***, oesophageal injury.
Skin and subcutaneous tissue disorders		Rash, pruritus, urticaria, angioedema, allergic dermatitis.

* Brown or black spots on teeth are reversible upon treatment discontinuation.

**According to data published in the literature, the lining of the stomach and gastrointestinal tract of patients receiving iron-based treatments may be pigmented, which may interfere with gastrointestinal surgery.

*** Patients with deglutition disorders may also be at risk of oesophageal lesions or of bronchial necrosis, in case of false route.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9. Overdose

Cases of overdose with iron salts have been reported, particularly in small children, by accidental ingestion. Ingestion of oral dose of 20 mg elemental iron/kg body weight or more can lead to intoxication symptoms. Ingestion of more than 60 mg/kg can result in severe toxicity. The equivalent of 200 to 250 mg elemental iron/kg is considered potentially fatal.

Acute iron poisoning can occur into five stages:

- In the first stage (0.5 to 6 hours), the patient mainly exhibits gastrointestinal symptoms including abdominal pain, vomiting, diarrhea, hematemesis, and hematochezia. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- The second stage (6 to 24 hours), which is not always seen, represents an apparent recovery phase, as the patient's gastrointestinal symptoms may resolve despite toxic amounts of iron absorption.
- The third stage (6 to 72 hours) is characterized by the recurrence of gastrointestinal symptoms, shock, and metabolic acidosis. Iron-induced coagulopathy, hepatic dysfunction, cardiomyopathy, and renal failure are also observed in this stage.
- The fourth stage (12 to 96 hours) is characterized by an elevation of aminotransferase levels and possible progression to hepatic failure.

- The fifth stage (2 to 8 weeks) represents the consequences of the healing of the injured gastrointestinal mucosa including pyloric or proximal bowel scarring and obstruction.

The progression from stage to stage may be very rapid, and not every patient goes through every stage.

Treatment consisting of gastric lavage with 1% sodium bicarbonate solution should be instituted as soon as possible. Depending on serum iron concentrations, use of a chelating agent may be recommended, the most specific being deferoxamine.

The administration of excessive doses of folic acid has been found to give rise to mental, gastrointestinal and sleep disorders. The dose of folic acid contained in TOTYLEM is very low and, therefore, the risk of toxicity associated with overdose is very low.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIANEMIC PREPARATIONS, ATC code: B03AD05.

RELATED TO IRON:

Iron is an essential mineral nutrient that plays a key role in many physiological functions such as oxygen transport, ATP production, DNA synthesis and electron transport.

Mechanism of action

Iron is the central atom of the haem groups embedded in haemoglobin and is also essential for erythropoiesis.

RELATED TO FOLIC ACID:

Mechanism of action

Folic acid (folate) acts as a co-enzyme in the transfer of carbon atoms in the biosynthesis of purine nucleotides and deoxythymidine monophosphate essential for the synthesis of DNA and RNA. In general, cell growth and multiplication require significant amounts of folic acid (folate): nervous system tissues and erythrocytes.

5.2. Pharmacokinetic properties

RELATED TO IRON:

Absorption

Iron absorption is an active process that occurs mainly in the duodenum and proximal jejunum. Absorption is increased when iron stores are decreased.

Iron absorption may be affected by concomitant use of certain foods, beverages or the co administration of certain medicinal products (see sections 4.4 and 4.5).

Distribution

In the body, iron is stored mostly in the bone marrow (erythroblasts) and

erythrocytes. Iron is stored in a complex as ferritin in the liver, spleen and bone marrow. In the bloodstream, iron is transported by transferrin, primarily to the bone marrow where it is incorporated into haemoglobin.

Biotransformation

Iron is a metal ion, not metabolized by the liver.

Elimination

Average iron excretion in healthy subjects is estimated at about 1 mg/day.

The main routes of elimination are the gastrointestinal tract (enterocyte shedding, haem degradation from erythrocyte extravasation), the urogenital tract and the skin.

RELATED TO FOLIC ACID:

Absorption

Folic acid (folate) is absorbed rapidly in the gastrointestinal tract, mainly in the proximal part of the small intestine.

Distribution

Folate is distributed throughout the body. The main storage site for folate is the liver. Folate is excreted into breast milk.

Biotransformation

Folate is transformed into an active metabolic form, 5 methyltetrahydrofolate (5 MTHF), in the plasma and liver. Folate metabolites undergo enterohepatic circulation.

Elimination

Folate metabolites are eliminated in the urine and excessive folate is excreted unchanged in urine.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

The different genotoxicity studies (micronucleus tests, chromosomal aberration assay) showed that folic acid have no specific genotoxic effect.

The overview conclusions of the genotoxicity studies performed on iron salts demonstrated that these salts may be cytotoxic and may induce apoptosis in proliferative cells at high concentrations (Ames test) but have no specific genotoxic effect (micronucleus assay).

According to different carcinogenicity studies conducted in mice and rats, no carcinogenic potential has been assessed with iron salts.

Folate has a dual effect on cancer: evidence indicates that an abundant intake of foodstuffs rich in folate conveys protection against the development of colorectal cancer , and perhaps some other common cancers as well ; and some observations in animal studies demonstrate that an overly abundant intake of folate among those who harbor existing foci of neoplasia might instead produce a paradoxical promotion of tumorigenesis: these effect have been observed only at exposures considered sufficiently in excess of the

maximum human exposure indicating little relevance to clinical use.

Finally, sufficient animal data on effects on reproduction of the active substances iron gluconate and folic acid are not available. Iron soluble salts has been reported as not toxic for reproduction (NOAEL 500 mg/kg/day for the dichloride salt), not toxic for dams and not embryotoxic or teratogenic at dose up to 200 mg/kg/day for the sulfate salt (NOAEL 500 mg/kg/day for the dichloride salt).

Folic acid was well tolerated at dose twenty times higher than the level considered adequate for pregnant rats (2 mg folic acid/kg diet) and corresponding to a dose about 40-fold higher than the therapeutic dose in human.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

Ascorbic acid
Hypromellose
Croscarmellose sodium
Magnesium stearate
Lactose monohydrate
Maize starch

Film-coating:

Hypromellose
Stearic acid
Microcrystalline cellulose
Titanium dioxide (E171)
Carmine Lake (E120)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5. Nature and contents of container

- 34009 302 766 5 5: 30 tablets in blister packs (PVC/PE/PVDC/Aluminium).
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6.6. Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratoire Innotech International
22 Avenue Aristide Briand
94110 Arcueil

8. MARKETING AUTHORISATION NUMBER(S)

CTD12916/26638

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05-11-2025

10. DATE OF REVISION OF THE TEXT

05-11-2025