1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

ZILATEC 150 mg (Ranitidine Tablets USP 150mg)

2. Qualitative and quantitative composition

Each film coated tablet contains:

Ranitidine Hydrochloride USP

Eq. To Ranitidine…….150 mg

Approved colours used in coating

3. Pharmaceutical form

Film-coated tablets

Orange coloured, round, biconvex, film coated tablets.

4. Clinical particulars

4.1 Therapeutic indications

Adults

Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.

Prevention of NSAID associated duodenal ulcers.

Treatment of duodenal ulcers associated with *Helicobacter pylori* infection.

Post-operative ulcer.

Oesophageal reflux disease including long term management of healed oesophagitis.

Symptomatic relief in gastro-oesophageal reflux disease.

Zollinger-Ellison syndrome.

Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but is not associated with the above conditions.

Prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.

Prophylaxis of recurrent haemorrhage with bleeding peptic ulcers.

Before general anaesthesia in patients at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

Children (3 to 18 years)

- Short term treatment of peptic ulcer

- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

4.2 Posology and method of administration

For oral administration.

Adults (including the elderly) / Adolescent (12 years and over):

The usual dosage is 150mg twice daily, taken in the morning and evening.

Duodenal ulcer, gastric ulcer:

The standard dosage regimen is 150 mg twice daily or 300 mg at night. It is not necessary to time the dose in relation to meals.

In most cases of duodenal ulcer, benign gastric ulcer and post operative ulcer, healing occurs in 4 weeks. Healing usually occurs after a further 4 weeks of treatment in those patients whose ulcers have not fully healed after the initial course of therapy.

Ulcers following NSAID therapy or associated with continued NSAIDs:

8 weeks' treatment may be necessary.

Prevention of NSAID associated duodenal ulcers:

150 mg twice daily may be given concomitantly with NSAID therapy.

In duodenal ulcer 300mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150mg twice daily or 300mg at night. The increased dose has not been associated with an increased incidence of unwanted effects.

Duodenal ulcers associated with *Helicobacter pylori* infection:

For duodenal ulcers associated with *Helicobacter pylori* infection, ranitidine 300 mg at bedtime or 150 mg twice daily may be given with oral amoxicillin 750 mg three times daily and metronidazole 500 mg three times daily for two weeks. Therapy with ranitidine should continue for a further two weeks. This dose regimen significantly reduces the frequency of duodenal ulcer recurrence.

Maintenance treatment at a reduced dosage of 150 mg at bedtime is recommended for patients who have responded to short term therapy, particularly those with a history of recurrent ulcer.

Gastro-oesophageal reflux disease:

Symptom relief in gastro-oesophageal reflux disease. In patients with gastro-oesophageal reflux disease, a dose regimen of 150 mg twice daily for 2 weeks is recommended and this can be repeated in patients in whom the initial symptomatic response is inadequate.

Oesophageal reflux disease

In the management of oesophageal reflux disease, the recommended course of treatment is either 150 mg twice daily or 300 mg at bedtime for up to 8 weeks or 12 weeks if necessary.

In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150mg four times daily for up to 12 weeks. The increased dose has not been associated with an increased incidence of unwanted effects.

Healed oesophagitis:

For long term treatment, the recommended adult oral dose is 150mg twice daily. Long-term treatment is not indicated in the management of patients with unhealed oesophagitis, with or without Barrett's epithelium.

Zollinger-Ellison syndrome

In patients with Zollinger-Ellison syndrome, the starting dose is 150mg three times daily and this may be increased as necessary. Patients with this syndrome have been given increasing doses up to 6 g daily and these doses have been well tolerated.

Chronic episodic dyspepsia:

For patients with chronic episodic dyspepsia the recommended course of treatment is 150mg twice daily for up to 6 weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration.

Prophylaxis of acid aspiration (Mendelson's syndrome):

In patients thought to be at risk of acid aspiration (Mendelson's) syndrome an oral dose of 150mg can be given 2 hours before induction of general anaesthesia, and preferably also 150mg the previous evening.

In obstetric patients at commencement of labour, an oral dose of 150mg may be given followed by 150mg at 6 hourly intervals. It is recommended that since gastric emptying and drug absorption are delayed during labour, any patient requiring emergency general

anaesthesia should be given, in addition, a non-particulate antacid (*eg* sodium citrate) prior to induction of anaesthesia. The usual precautions to avoid acid aspiration should also be taken.

Children 12 years and over

For children 12 years and over the adult dosage is given.

Children from 3 to 11 years and over 30 kg of weight

See Section 5.2 Pharmacokinetic Properties - Special Patient Populations.

Peptic Ulcer Acute Treatment

The recommended oral dose for the treatment of peptic ulcer in children is 4mg/kg/day to 8mg/kg/day administered as two divided doses to a maximum of 300mg ranitidine per day for a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs after eight weeks of treatment.

Gastro-Oesophageal Reflux

The recommended oral dose for the treatment of gastro-oesophageal reflux in children is 5mg/kg/day to 10mg/kg/day administered as two divided doses to a maximum dose of 600mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).

Neonates

Safety and efficacy in new-born patients has not been established.

Patients over 50 years of age

See Section 5.2 Pharmacokinetic Properties (Special Patient Populations, Patients over 50 years of age)

Renal Impairment:

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min). Accordingly, it is recommended that the daily dose of ranitidine in such patients should be 150 mg at night for 4-8 weeks. The same dose should be used for maintenance treatment, if necessary. If an ulcer has not healed after treatment, 150 mg twice daily dosage should be instituted followed, if need be, by maintenance treatment of 150 mg at night.

4.3 Contraindications

Ranitidine products are contraindicated in patients known to have hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer [and if indications include dyspepsia; patients of middle age and over with new or recently changed dyspeptic symptoms must be included] as treatment with ranitidine may mask symptoms of gastric carcinoma.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment.

The dosage should be adjusted as detailed above in section 4.2 in Renal impairment.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

In patients such as the elderly, persons with chronic lung disease, diabetes or the immuno-compromised, there may be an increased risk of developing community acquired pneumonia.

A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of ranitidine alone versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI, 1.26-2.64). Post-marketing data indicate reversible mental confusion, depression, and hallucinations have been reported most frequently in severely ill and elderly patients (see section 4.8).

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly and in those with a history of peptic ulcer.

4.5 Interaction with other medicinal products and other forms of interaction

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system:

Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:

Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3) Alteration of gastric pH:

The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

There is no evidence of an interaction between ranitidine and amoxicillin or metronidazole.

If high doses (2 g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effects of ranitidine on human fertility. There were no effects on male and female fertility in animal studies (see section 5.3).

Pregnancy

Ranitidine crosses the placenta. Like other drugs ranitidine should only be used during pregnancy if it is considered essential.

Lactation

Ranitidine is excreted in human breast milk. Like other drugs ranitidine should only be used during breast-feeding if considered essential.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects: Very common (> 1/10), Common > 1/100 to < 1/10), Uncommon >1/1,000 to < 1/100) Rare (> 1/10,000 to < 1/1,000), Very rare (< 1/10,000), not known (frequency cannot be estimated from the available data).

Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood & Lymphatic System Disorders

Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. A granulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

Immune System Disorders

Rare: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).

Very Rare: Anaphylactic shock

Unknown: dyspnoea

These events have been reported after a single dose.

Psychiatric Disorders

Very Rare: Reversible mental confusion, depression and hallucinations.

These have been reported predominantly in severely ill patients, in elderly and in nephropatic patients.

Nervous System Disorders

Very Rare: Headache (sometimes severe), dizziness and reversible involuntary movement disorders.

Eye Disorders

Very Rare: Reversible blurred vision.

There have been reports of blurred vision, which is suggestive of a change in accommodation.

Cardiac Disorders

Very Rare: As with other H2 receptor antagonists bradycardia, A-V block and tachycardia (for all formulations).

Vascular Disorders

Very Rare: Vasculitis.

Gastrointestinal Disorders

Very Rare: Acute pancreatitis, diarrhoea

Uncommon: abdominal pain, , constipation, nausea (these symptoms mostly improved during continued treatment).

Hepatobiliary Disorders

Rare: Transient and reversible changes in liver function tests.

Very Rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

Skin and Subcutaneous Tissue Disorders

Rare: Skin rash.

Very Rare: Erythema multiforme, alopecia.

Musculoskeletal and Connective Tissue Disorders

Very Rare: Musculoskeletal symptoms such as arthralgia and myalgia.

Renal and Urinary Disorders

Very rare: Acute interstitial nephritis.

Rare: elevation of plasma creatinine (usually slight; normalised during continued treatment)

Reproductive System and Breast Disorders

Very Rare: Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea)

Paediatric population:

The safety of ranitidine has been established in children aged 0-16 years with gastric acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited safety data available on long-term use, in particular in relation to growth and development.

Reporting of suspected adverse reactions

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.

4.9 Overdose

Symptoms and Signs

Ranitidine is very specific in action and no particular problems are expected following overdosage with ranitidine formulations.

Treatment

Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism ATC Code: AO2 BA02 Ranitidine is a specific, rapidly acting histamine H2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Ranitidine has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours. Although no clear casual link has been established, a large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 – 2.48). Therefore, in patients with conditions predisposing to the development of pneumonia, such as chronic lung disease, diabetes, or the immunocompromised, there may be an increased risk of developing community acquired pneumonia.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1—3 hours. Two distinct peaks or plateau in the absorption phase result from reabsorption of drug excreted into the intestine. The absolute bioavailability of ranitidine is 50-60% and plasma concentrations increase proportionally with increasing dose up to 300 mg.

Distribution

Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism

Ranitidine is not extensively metabolised. The fraction of the dose recovered as metabolites is similar after both oral and i.v. dosing; and includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1 to 2% as the furoic acid analogue.

Elimination

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2-3 hours. The major route of elimination is renal. After IV administration of 150 mg 3H-ranitidine, 98% of the dose was recovered, including 5% in faeces and 93% in urine, of which 70% was unchanged parent drug. After oral administration of 150 mg 3H-ranitidine, 96% of the dose was recovered, 26% in faeces and 70% in urine of which 35% was unchanged parent drug. Less than 3% of the dose is excreted in bile. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Special Patient Populations

Children (3 years and above)

Limited pharmacokinetic data have shown that there are no significant differences in half-life (range for children 3 years and above: 1.7 - 2.2 h) and plasma clearance (range for children 3 years and above: 9 - 22ml/min/kg) between children and healthy adults receiving oral ranitidine when correction is made for body weight.

Patients over 50 years of age

In patients over 50 years of age, half-life is prolonged (3-4 h) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

5.3 Preclinical safety data

Extensive studies have been carried out in animals. The pharmacology of ranitidine hydrochloride shows it to be a surmountable H2 receptor antagonist which produces an inhibition of gastric acid secretion. Extensive toxicological investigations have been

conducted which predicted a very safe profile for clinical use. This safety has since been confirmed by extensive use in patients for many years.

6. Pharmaceutical particulars

6.1 List of excipients

1. Microcrystalline Cellulose (PH-102)
2. Microcrystalline Cellulose
3. Magnesium Stearate
4. Colloidal Anhydrous Silica
5. Croscarmellose Sodium
6. Sodium Starch Glycolate
7. Purified Talc
8. Calcium Hydrogen Phosphate
9. Citric Acid
10. Sodium Lauryl Sulfate
11. Instamoistshield Orange (IC-MS-4020)
12. Isopropyl Alcohol
13. Dichloromethane
14. Hypromellose
15. Titanium Dioxide

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

Available in packs of 2 X 10, 10 X 10 and 20 X 10 Alu/ Alu strip packed in carton along with package insert.

6.6 Special precautions for disposal and other handling

No special requirements

7. Manufactured by:

Name: Brawn Laboratories Limited.

Location (address): 13, N.I.T. Industrial Area,

FARIDABAD-121 001, (HARYANA)

Country: INDIA

Telephone fax Tel: +91-129-4360113

Website: www.brawnlabs.com

8. Marketing Authorisation Number

N/A

9. Date of First Authorisation/Renewal of Authorisation

N/A

10. Date of (Partial) Revision of the Text:

N/A

11. Dosimetry (If Applicable):

Not Applicable

12. Instruction for preparation of radiopharmaceutical (If Applicable)

Not Applicable