1 NAME OF THE MEDICINAL PRODUCT
Inside Brus 150 mg effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each effervescent tablet contains:
ranitidine hydrochloride corresponding to 150 mg ranitidine.

Excipients with known effect
Lactose monohydrate 250 mg
Sorbitol 0.7 mg
Aspartame 5.0 mg
Sodium 402 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Effervescent tablet
Yellow tablet with slight speckles, round, smooth, with a breaking notch on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Duodenal ulcers, benign gastric ulcers, verified by e.g. endoscopy and histology, reflux oesophagitis
and Zollinger-Ellison syndrome. Symptomatic short-term treatment of heartburn and acid eructations
in gastro-oesophageal reflux disease.
Maintenance therapy for patients with reflux oesophagitis.
Prophylactic treatment of duodenal ulcers to prevent their recurrence.

4.2 Posology and method of administration
Adults:
The normal dose for duodenal and gastric ulcers is 300 mg per day, either 300 mg at night or 150 mg
morning and evening. The dose may be increased to 300 mg morning and evening as necessary.
The normal duration of treatment is 4 weeks but with isolated patients, e.g. those with current NSAID
therapy, a period of 8 weeks treatment gives better healing of the ulcer.

For prophylactic treatment the normal dose is 150 mg in the evening.

For reflux oesophagitis the normal dose is 150 mg morning and evening, alternatively 300 mg at night
for 4-8 weeks, but the dosage and duration of treatment should be individualised according to the
severity of the illness. In severe cases the daily dose may be increased up to 600 mg in divided doses.

For maintenance therapy 150 mg morning and evening is recommended. Before a long-term treatment
of reflux oesophagitis, the diagnosis has to be confirmed by endoscopy.
For symptomatic gastro-oesophageal reflux disease the normal dose is 150 mg morning and evening, alternatively 1 tablet when necessary, but maximum 2 tablets per day. If the symptoms have not disappeared after 2-4 weeks treatment, the patient should go through further investigation.

For Zollinger-Ellison syndrome the initial dose is 150 mg 3 times daily, but this may be increased when necessary.

Children:
Experience of ranitidine in the treatment of children is limited. If reduction of gastric juice secretion is considered desirable, 5 mg/kg body weight should be given.

Impaired renal function:
The half-life in plasma is prolonged in case of impaired renal function. The dosage should therefore be halved in cases of markedly impaired renal function (creatinine clearance 5 – 50 ml/min.). In that case 150 mg may be given perorally at night.

The effervescent tablet is rapidly dissolved in half a glass of water and gives a clear, yellow orange solution.

Ranitidine is eliminated from the body during haemodialysis. A patient receiving dialysis should therefore take ranitidine after each session of dialysis.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Caution should be exercised in patients with impaired renal function, severe hepatic disease or acute porphyria. Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria

Suspected ulcer disease must be objectively verified at an early stage by x-ray or endoscopy to avoid inadequate treatment.

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 severe renal impairment. The dosage should be adjusted as detailed above under Posology and method of administration in section 4.2 in renal impairment.

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, 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). This increased risk was mainly observed in patients with pulmonary diseases, diabetes, heart failure and in immunocompromised patients.
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.

This medicinal product contains 402 mg sodium per effervescent tablet, equivalent to 21% of the WHO recommended maximum daily intake for sodium.
The maximum daily dose of this product is equivalent to 80% of the WHO recommended maximum daily intake for sodium.
Inside Brus is considered high in sodium content. This should be particularly taken into account for those on a low salt diet. Caution should be exercised in case of hypertension, cardiovascular insufficiency.

This medicinal product contains 5 mg aspartame in each effervescent tablet. Aspartame is metabolised to phenylalanine; important only for patients with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infant below 12 weeks of age.

This medicinal product contains 0.7 mg sorbitol in each effervescent tablet.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Inside Brus contains lactose (as lactose monohydrate 250 mg in each effervescent tablet). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Alteration of gastric pH:
The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam [with 30%, which may elevate the effects], midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delavirdine, gefitinib, erlotinib). Concomitant administration of 300 mg ranitidine and erlotinib decreased erlotinib exposure (AUC) and maximum concentrations ($C_{\text{max}}$) by 33% and 54% respectively. However, when erlotinib was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d, erlotinib exposure (AUC) and maximum concentrations ($C_{\text{max}}$) decreased only by 15% and 17% respectively.
2. Inhibition of cytochrome P450-system:
Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine and propranolol.
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. There are several case reports of increased plasma concentrations of theophylline. Although the interaction has not been observed in a number of clinical studies, available information cannot preclude that an interaction may occur in some individuals. There have also been reports of increased plasma concentrations of phenytoin.
3. 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.
The clinical significance of following interactions is not yet established:

**Alcohol**
The plasma concentration and effect of alcohol may rise with concomitant intake of ranitidine and moderate amounts of alcohol.

**Sucralfate**
The administration of sucralfate, in high doses (2g), has been associated with a decrease in the absorption of ranitidine. This does not occur if sucralfate is taken within 2 hours after dosing with ranitidine.

**Antacids**
A decrease in the bioavailability of ranitidine occurs in the event of concomitant administration of antacids.

**Amprenavir**
Serum levels of amprenavir can be reduced by concomitant use of ranitidine. Concurrent administration of ranitidine (300 mg single dose) with fosamprenavir (1400 mg single dose) decreased plasma amprenavir AUC by 30 % and C\text{max} by 51 %. There was, however, no change observed in the amprenavir C\text{min} (C\text{12h}). No dose adjustment for any of the respective medicinal products is considered necessary when H2 receptor antagonists are administered concomitantly with fosamprenavir.

**Saquinavir**
In a study in 12 healthy male volunteers there was an increase in exposure of saquinavir when saquinavir was dosed in the presence of both ranitidine and food, relative to saquinavir dosed with food alone. This resulted in AUC values of saquinavir, which were 67 % higher. This increase is not thought to be clinically relevant and no dose adjustment of saquinavir is recommended.

### 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 considered essential.

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

### 4.7 Effects on ability to drive and use machines

Side effects such as dizziness and fatigue may occur and this should be considered in connection with, for example, driving and other work requiring precision.

### 4.8 Undesirable effects

The incidence of undesirable effects is defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>Very rare</td>
<td>Blood count changes (leucopenia, thrombocytopenia). These are usually reversible.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Agranulocytosis or pancytopenia sometimes with marrow hypoplasia or marrow aplasia.</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Rare</td>
<td>Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Anaphylactic shock</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dyspnoea.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>These events have been reported after a single dose.</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>Very rare</td>
<td>Reversible mental confusion, depression and hallucinations. These adverse reactions have been reported predominantly in severely ill patients, in the elderly and in nephropatic patients.</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very rare</td>
<td>Headache (sometimes severe), dizziness and reversible involuntary movement disorders. Tremor and myoclonies.</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Very rare</td>
<td>Reversible blurred vision.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There have been reports of blurred vision, which is suggestive of a change in accommodation.</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Very rare</td>
<td>Bradycardia, AV-block, tachycardia.</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Very rare</td>
<td>Vasculitis.</td>
</tr>
<tr>
<td>Disorder Type</td>
<td>Frequency</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very rare</td>
<td>Acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Abdominal pain, diarrhoea, constipation, nausea (these symptoms mostly improved during continued treatment.)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
<td>Transitional changes in liver function tests.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver failure (fatal cases have been reported).</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rare</td>
<td>Skin rash.</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Erythema multiforme, alopecia.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Contact dermatitis.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Arthralgia, myalgia.</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very rare</td>
<td>Acute interstitial nephritis.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Elevated plasma-creatinine (usually slight; normalised during continued treatment).</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Very rare</td>
<td>Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).</td>
</tr>
<tr>
<td>General disorders and administration site disorders</td>
<td>Common</td>
<td>Fatigue.</td>
</tr>
</tbody>
</table>

**Paediatric population**

The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited long term safety data available, in particular regarding 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in

(To be completed nationally).

### 4.9 Overdose

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

7.5 g to an adult gave no or mild intoxication. 2.5 mg 4 times daily to 3-months-old child gave opisthotonus. 150 mg to a 3-year-old gave no symptoms. Bradycardia and dyspnoea are described. Uncoordinated muscular activity, cramps.

**Treatment**
Symptomatic and supportive therapy should be given as appropriate. Initially charcoal may be given. Atropine may be tried in the case of bradycardia. If necessary, ranitidine may be removed from plasma by haemodialysis.

### 5  PHARMACOLOGICAL PROPERTIES

#### 5.1  Pharmacodynamic properties

Pharmacotherapeutic group: Acid-inhibiting substance - H$_2$-antagonist  
ATC code: A02BA02

Ranitidine, a chemically substituted amino alkyl furan, is an H$_2$-receptor antagonist, which competitively blocks the effect of histamine on H$_2$-receptors. In this situation, basal and stimulated gastric juice secretion is inhibited both in volume and in hydrochloric acid content. As a result of reduction of the volume of gastric juice the total pepsinogenic secretion is also reduced.

#### 5.2  Pharmacokinetic properties

Bioavailability is approx. 50 %. Absorption is not affected by food. Maximum plasma concentration is reached 2-3 hours after a peroral dose of 150 mg. Despite large individual variation there is a connection between the serum ranitidine concentration and the inhibition of acid secretion. A serum concentration of approx. 100 microgram/l gives approx. 50 % inhibition of stimulated acid secretion over a period of approx. 8 hours. Following a peroral single dose of 150 mg ranitidine an inhibition of hydrochloric acid secretion has been observed for up to 12 hours. In patients with impaired renal function the half-life is prolonged.

In the case of severe reduced hepatic function first-pass metabolism of ranitidine is reduced, which results in a moderately elevated bioavailability and serum concentration. Ranitidine is partially excreted in the urine, approx. 40 % of a given dose after peroral intake. Approx. 10 % of a given dose is excreted as biologically inactive metabolites, while the remainder consists of unmetabolized ranitidine. Absorption is more rapid with an effervescent tablet than with a normal tablet.

#### 5.3  Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, general toxicity, reproduction effects, genotoxicity and carcinogenicity.

### 6  PHARMACEUTICAL PARTICULARS

#### 6.1  List of excipients

- Sodium cyclamate
- Aspartame
- Lactose monohydrate
- Saccharin sodium
- Citric acid
Sodium hydrogen carbonate
Sodium carbonate anhydrous
Sorbitol
Mannitol
Simeticone
Sodium citrate
Curcumin (colouring agent E 100)
Fruit flavour (sorbitol, mannitol, silica colloidal anhydrous, glucono-lactone, powder flavour orange, natural orange oil, mandarin oil, maltodextrine)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original container in order to protect from moisture.
Do not store above 30˚C.

6.5 Nature and contents of container

Tubes of polypropylene
The tubes are closed with a stopper which contains a desiccant.

Pack size:
10 tabs (1 tube of 10)
20 tabs (2 tubes of 10)
30 tabs (3 tubes of 10)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Meda OTC AB
Box 906
170 09 Solna
Sweden

8 MARKETING AUTHORISATION NUMBER

15435
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 March 2000
Date of last renewal: 29 July 2008

10 DATE OF REVISION OF THE TEXT

2019-10-10