

# **Public Assessment Report**

## **Decentralised**

**Ranitidine 50mg/2ml  
solution for injection or infusion**

**UK/H/893/01/DC**

**Beacon Pharmaceuticals**

**Lay Summary**

The MHRA granted a market authorisation (Licence) to Beacon Pharmaceuticals Ltd for the medicinal product Ranitidine 50mg/2ml solution for injection and infusion (PL 18157/0019) on 21/10/2008. The product is a prescription only medicine.

Ranitidine is used in the treatment and prevention of peptic ulcers and associated conditions. The product was demonstrated to be a generic medical product of the reference product *Zantac*® Injection 50 mg/ 2ml ampoule by GlaxoSmithKline.

## TABLE OF CONTENTS

Module 1: Information about initial procedure	Page	4
Module 2: Summary of Product Characteristics	Page	5
Module 3: Product Information Leaflets	Page	10
Module 4: Labelling	Page	14
Module 5: Scientific Discussion	Page	16
1 Introduction		
2 Quality aspects		
3 Non-clinical aspects		
4 Clinical aspects		
5 Overall conclusions		
Module 6      Steps take after initial procedure	Page	19

## Module 1

<b>Product Name</b>	Ranitidine 50mg/2ml solution for injection or infusion
<b>Type of Application</b>	Standard Abridged Decentralised (Article 10.1)
<b>Active Substance (INN)</b>	Ranitidine
<b>Pharmacotherapeutic Classification (ATC)</b>	A02BA02
<b>Pharmaceutical Form and Strength</b>	Solution for Injection and Infusion 50mg/2ml
<b>Procedure Numbers</b>	<b>UK/H/893/01/DC</b>
<b>RMS</b>	UK
<b>CMS</b>	<b>Ireland</b>
<b>Start Date</b>	26/04/2006
<b>End Date</b>	21/10/2008
<b>MA Number</b>	PL 18157/0019
<b>Name and address of MA holder</b>	Beacon Pharmaceuticals Ltd, 85 High Street, Tunbridge Wells, Kent TN1 1YG, UK.

## Module 2

### Summary of Product Characteristics

#### 1. NAME OF THE MEDICINAL PRODUCT

Ranitidine 50mg/2ml Solution for Injection and Infusion

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each one ml of solution contains 25mg ranitidine as ranitidine hydrochloride. Each 2ml ampoule contains 50mg ranitidine.

For a full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Solution for Injection and Infusion

Clear, colourless solution.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Ranitidine Solution for Injection is indicated for the treatment of duodenal ulcer, benign gastric ulcer, post - operative ulcer, and of Zollinger - Ellison Syndrome.

In the management of conditions where reduction of gastric secretion and acid output is desirable, such as reflux oesphagitis.

As prophylaxis against:

- gastrointestinal haemorrhage from stress ulceration in seriously ill patients
- recurrent haemorrhage in patients with bleeding peptic ulcers
- acid aspiration (Mendelson's Syndrome) before anaesthesia in patients at risk, particularly obstetric patients during labour.

##### 4.2 Posology and method of administration

For intravenous or intramuscular injection or, after dilution, for intravenous infusion. Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Adults (including elderly)

Ranitidine Solution for Injection may be given as:

- a slow intravenous injection (over at least two minutes) of 50 mg, after dilution to a volume of 20 ml per 50 mg dose. This dose may be repeated every six to eight hours
- an intermittent intravenous infusion at a rate of 25 mg per hour for two hours. The infusion may be repeated at six to eight hour intervals
- an intramuscular injection of 50 mg (2ml) every six to eight hours.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, parenteral administration may be continued until oral feeding commences. Patients considered to be still at risk may then be treated orally with tablets 150 mg twice daily.

In the prophylaxis of upper gastro-intestinal haemorrhage from stress ulceration in seriously ill patients a priming dose of 50 mg as a slow intravenous injection followed by a continuous intravenous infusion of 0.125 - 0.250 mg/kg/hr may be preferred.

In patients considered at risk of developing acid aspiration (Mendelson's) syndrome, Ranitidine Solution for Injection 50 mg may be given intramuscularly or by slow intravenous injection (over 2 minutes), 45 to 60 minutes before induction of general anaesthesia.

#### Children

The use of Ranitidine Solution for Injection in children has not been evaluated.

#### Renal Impairment

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with severe renal impairment (creatinine clearance less than 50ml/min). It is recommended in such patients that Ranitidine Solution for Injection be administered in doses of 25mg.

### **4.3 Contraindications**

Hypersensitivity to the active substance(s) or to any of the excipients.

### **4.4 Special warnings and precautions for use**

Treatment with a histamine H<sub>2</sub>-antagonist may mask the symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with ranitidine is started.

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 in Section 4.2 Posology and Method of Administration.

Asystole and bradycardia in association with rapid administration of ranitidine has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

It has been reported that the use of higher than recommended doses of intravenous H<sub>2</sub>-antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

Although clinical reports of acute intermittent porphyria associated with ranitidine administration have been rare and inconclusive, ranitidine should be avoided in patients with a history of this condition.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Ranitidine, at blood levels produced by standard doses, does not inhibit or interact significantly with the hepatic cytochrome P450-linked mixed function oxygenase system.

Accordingly, ranitidine in usual therapeutic doses, does not potentiate the actions of drugs which are inactivated by this enzyme; these include diazepam, lidocaine, phenytoin, propranolol, theophylline and warfarin.

To date interactions of ranitidine have not been shown with warfarin, barbiturates or diazepam.

#### **4.6 Pregnancy and lactation**

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section have been without any adverse effect on labour, delivery or subsequent neonatal progress. Ranitidine is also excreted in human breast milk. Like other drugs, ranitidine should only be used during pregnancy or lactation if considered essential by a physician.

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

None known.

#### **4.8 Undesirable effects**

The following convention has been utilised for the classification of undesirable effects: very common ( $>1/10$ ), common ( $>1/100$ ,  $<1/10$ ), uncommon ( $>1/1000$ ,  $<1/100$ ), rare ( $>1/10,000$ ,  $<1/1000$ ), very rare ( $<1/10,000$ ).

##### **Blood & Lymphatic System Disorders**

Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis 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

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 and elderly 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 H<sub>2</sub> receptor antagonists bradycardia and A-V Block.

#### **Vascular Disorders**

Very Rare: Vasculitis.

#### **Gastrointestinal Disorders**

Very Rare: Acute pancreatitis. Diarrhoea.

#### **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.

#### **Reproductive System and Breast Disorders**

Very Rare: Reversible impotence. Breast symptoms in men.

## **4.9 Overdose**

Ranitidine is very specific in action and accordingly, no particular problems are expected following overdosage with the drug. Symptomatic and supportive therapy should be given as appropriate. Ranitidine may be removed by haemodialysis.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: drugs for peptic ulcer and gastro-oesophageal reflux disease. H<sub>2</sub> – receptor antagonist.

ATC code: A02B A02

Ranitidine is a specific, rapidly acting histamine H<sub>2</sub>-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume, and the acid and pepsin content of the secretion.

### **5.2 Pharmacokinetic properties**

Absorption of ranitidine after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration. Ranitidine is not extensively metabolised. The elimination of the drug is primarily by tubular secretion. The elimination half-life of ranitidine is 2-3 hours. In studies with 150mg 3H-ranitidine, 93% of an intravenous dose was excreted in urine and



5% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose was eliminated unchanged. About 6% of the dose is excreted in the urine as the N-oxide, 2% as desmethyl ranitidine and 1-2% as the furoic acid analogue.

### **5.3 Preclinical safety data**

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Potassium dihydrogen phosphate

Disodium hydrogen phosphate dihydrate

Sodium chloride

Water for Injections

### **6.2 Incompatibilities**

None

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Do not store above 25°C. Keep ampoules in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

2 ml solution in amber, type 1 glass ampoules.

Pack size: 5 ampoules

### **6.6 Special precautions for disposal and other handling**

Ranitidine Injection has been shown to be compatible with the following intravenous infusion fluids:

Sodium Chloride 0.9% w/v

Dextrose 5% w/v

Sodium Chloride 0.18% w/v and Dextrose 4% w/v

Sodium Bicarbonate 4.2% w/v

Hartmann's solution

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user

and would normally not be longer than 24 hours at 2 to 8°C, unless preparation of solutions has taken place in controlled and validated aseptic conditions.  
All solutions of Ranitidine Solution for Injection should be discarded after use.

## **7. MARKETING AUTHORISATION HOLDER**

Beacon Pharmaceuticals Ltd  
85 High Street  
Tunbridge Wells  
Kent TN1 1YG  
UK

## **8. MARKETING AUTHORISATION NUMBER(S)**

PL 18157/0019

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

21 October 2008

## **10. DATE OF REVISION OF THE TEXT**

November 2007

## Module 3

# Product Information Leaflet

### PACKAGE LEAFLET: INFORMATION FOR THE USER

#### Ranitidine 50mg/2ml Solution for Injection and Infusion

Read all of this leaflet carefully before you are given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

#### In this leaflet:

1. What Ranitidine Injection is and what it is used for
2. Before you receive Ranitidine Injection
3. How Ranitidine Injection will be given
4. Possible side effects
5. Storing Ranitidine Injection
6. Further information

The name of this medicine is **Ranitidine 50mg/2ml Solution for Injection and Infusion** (referred to as **Ranitidine Injection** throughout this leaflet).

#### 1. WHAT RANITIDINE INJECTION IS AND WHAT IT IS USED FOR.

Ranitidine Injection is a solution for injection or infusion into a vein, or injection into a muscle. It contains ranitidine as the active ingredient.

Ranitidine is one of a group of medicines called H<sub>2</sub>-antagonists that reduce the amount of acid in the stomach.

**It is used in adults (including the elderly) to:**

- Treat ulcers of the stomach or duodenum (the stomach empties into this part of the intestine)
- Treat problems caused by acid in the gullet (oesophagus)
- Prevent ulcers from bleeding
- Prevent acid coming up from the stomach during the anaesthetic given before a surgical operation.

#### 2. BEFORE YOU RECEIVE RANITIDINE INJECTION

**Ranitidine Injection should NOT be used if:**

- You are allergic (hypersensitive) to ranitidine or to any of the other ingredients (listed in Section 6, overleaf).

**Before receiving Ranitidine Injection, tell your doctor if:**

- Your kidneys are not working properly
- You have a current heart problem or a history of heart trouble
- You are pregnant or think you may be pregnant
- You are breast-feeding your baby
- You have a rare condition called porphyria
- You have any unintentional weight loss associated with acid indigestion

Talk to your doctor or nurse if any of these statements are currently applicable or were previously applicable to you.

#### **Taking Ranitidine Injection with other medicines**

Tell your doctor if you are taking or have recently taken any other medicines, including those obtained without a prescription.

#### **Pregnancy and breast-feeding**

As with other medicines it is not recommended that Ranitidine Injection be used during pregnancy or breast-feeding unless absolutely necessary.

#### **Driving and using machines**

Ranitidine Injection is unlikely to affect your ability to drive or operate machinery.

#### 3. HOW RANITIDINE INJECTION WILL BE GIVEN

Your doctor will decide the correct dose of Ranitidine Injection for you.

**Adults (including the elderly):** The usual dose is 50mg every 6 or 8 hours

This can be given by the doctor or nurse in one of three ways:

- By slow injection into a vein over 2 minutes (after dilution to a volume of 20mls)
- By means of a 'drip' (infusion) into a vein (given over 2 hours)
- By injection into a muscle

For patients at risk of acid coming up from the stomach during anaesthesia, Ranitidine Injection may be given by injection into a muscle or by slow injection into a vein, 45 to 60 minutes before the anaesthetic.

**Children:** The use of Ranitidine Injection is not recommended, as the safety and efficacy of use in children has not been established.



**Kidney impairment:** If your kidneys are not working properly your doctor may give you a lower dose.

If you have the impression that the effect of Ranitidine Injection is too strong or too weak, talk to your doctor. If you receive too much it is unlikely to cause any problems.

If you have any further questions on the use of this product, ask your doctor or nurse.

Some discolouration of the solution may occur on exposure to light. The solution should be inspected for this deterioration when drawing a dose from the ampoule.

#### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Ranitidine Injection can cause side effects, although not everybody gets them.

**A few people can be allergic to some medicines. If any of the following happen, tell your doctor or nurse immediately:**

- Severe itching of the skin, rash
- Chest tightness
- Swelling of the hands, feet, ankles, face, lips, tongue, mouth or throat, which may cause difficulties in swallowing or breathing.
- Collapse

You may have had a serious allergic reaction to Ranitidine Injection.

All of these are very serious side effects and are rare

#### **Tell your doctor if you notice any of the following:**

*Side effects that are rare (less than 1 in 1000 but more than 1 in 10,000)*

- Skin rash

*Side effects that are very rare (less than 1 in 10,000):*

- Confusion, depression, hallucinations (mainly reported in severely ill or elderly patients)
- Blood disorders that may result in unusual tiredness, shortness of breath, more infections than usual, bruising more easily
- Headache (sometimes severe), dizziness, uncontrolled movements
- Blurred vision
- Heart problems (slow or irregular heart rhythm)
- Inflammation of the blood vessels which may cause reddening of areas of skin, localised pain and tenderness
- Diarrhoea, inflammation of the pancreas (which may cause severe stomach pain)

- Liver problems which may lead to jaundice (yellow colour of skin and the whites of eyes)
- Red blotches or lumps on the skin, hair loss
- Pain in the joints or muscles
- Kidney problems that may cause changes in the amount and colour of water you pass
- If you are a man, sexual impotence that is normally reversible, tenderness of the breast and/or breast enlargement.

Many of these side effects are reversible and go away once ranitidine treatment is stopped.

If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or nurse.

#### 5. STORING RANITIDINE INJECTION

Do not store above 25°C

Keep ampoules in the carton to protect them from light.

Keep out of the reach and sight of children.

Ranitidine Injection should not be used after the expiry date on the ampoule and carton. The expiry date refers to the last day of that month.

#### 6. FURTHER INFORMATION

##### **What Ranitidine Injection contains**

The active substance is ranitidine. One 2ml ampoule contains 50mg of ranitidine as ranitidine hydrochloride.

Other ingredients are sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate dihydrate and water for injections.

##### **What Ranitidine Injection looks like and contents of the pack**

Ranitidine Injection is a clear, colourless liquid in amber glass ampoules.

Each carton of Ranitidine Injection contains 5 ampoules.

##### **Marketing Authorisation Holder**

Beacon Pharmaceuticals Ltd., 85 High Street, Tunbridge Wells, Kent TN1 1YG.

##### **Manufacturer**

Kleva S A, 189 Parnithos Avenue, 136 71 Acharnia, Athens, Greece.

**This leaflet was last approved in**



**The following information is intended for medical or healthcare professionals only:**

**Technical Leaflet**

**Ranitidine 50mg/2ml Solution for Injection and Infusion**

**Please read this information carefully before using Ranitidine 50mg/2ml Solution for Injection and Infusion (referred to as Ranitidine Injection throughout this leaflet). Further information is contained in the Summary of Product Characteristics.**

**Presentation**

Each 2ml ampoule of Ranitidine Injection contains 50mg of ranitidine as ranitidine hydrochloride. Product provided in amber glass ampoules, 5 ampoules in a carton.

**Indications**

Ranitidine Solution for Injection is indicated for the treatment of duodenal ulcer, benign oesophageal or gastric ulcer, post-operative ulcer, and of Zollinger - Ellison Syndrome.

In the management of conditions where reduction of gastric secretion and acid output is desirable, such as reflux oesophagitis.

As prophylaxis against:

gastrointestinal haemorrhage from stress ulceration in seriously ill patients

recurrent haemorrhage in patients with bleeding peptic ulcers acid aspiration (Mendelson's Syndrome) before anaesthesia in patients at risk, particularly obstetric patients during labour.

**Dosage and Method of Administration**

Whenever solution and container permit, parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

For intravenous or intramuscular injection or, after dilution, for intravenous infusion Ranitidine Injection should be injected either as a slow bolus injection or as a short term infusion lasting

15 minutes, directly into a large vein through a large-gauge needle or intravenous catheter.

Recommended rates of administration should not be exceeded as bradycardia in association with rapid administration of ranitidine has been reported rarely.

Adults (including elderly)

Ranitidine Injection may be given as a slow (over at least two minutes) intravenous injection of 50 mg after dilution to a volume of 20 ml per 50mg dose, which may be repeated every six to eight hours

an intermittent intravenous infusion at a rate of 25 mg per hour for two hours, which may be repeated at six to eight hour intervals

as an intramuscular injection of 50 mg (2ml) every six to eight hours.

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration, parenteral administration may be continued until oral feeding commences.

In the prophylaxis of upper gastro-intestinal haemorrhage from stress ulceration in seriously ill patients a priming dose of 50 mg as a slow intravenous injection followed by a continuous intravenous infusion of 0.125 - 0.250 mg/kg/hr may be preferred.

In patients considered to be at risk of developing acid aspiration (Mendelson's) syndrome, Ranitidine Solution for Injection 50 mg may be given intramuscularly or by slow intravenous injection (over 2 minutes) 45 to 60 minutes before induction of general anaesthesia.

Patients with renal impairment: Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with severe renal impairment (creatinine clearance less than 50ml/min). Accordingly, it is recommended in such patients that ranitidine be administered in doses of 25 mg.

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Children: The use of Ranitidine Injection in children has not been evaluated.

Ranitidine Injection has been shown to be compatible with the following intravenous infusion fluids:

0.9% Sodium Chloride BP, 5% Dextrose BP, 0.18% Sodium Chloride and 4% Dextrose BP, 4.2% Sodium Bicarbonate BP, Hartmann's solution

All unused mixtures of Ranitidine Solution for Injection with infusion fluids should be discarded.

#### **Contraindications**

Hypersensitivity to ranitidine or to any of the excipients.

#### **Special warnings and precautions for use**

Treatment with a histamine H<sub>2</sub>-antagonist may mask the symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with ranitidine is instituted.

It has been reported that the use of higher than recommended doses of intravenous H<sub>2</sub>-antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

Asystole and bradycardia in association with rapid administration of ranitidine has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

Although clinical reports of acute intermittent porphyria associated with ranitidine administration have been rare and inconclusive, ranitidine should be avoided in patients with a history of this condition.

#### Pregnancy and lactation

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section have been without any adverse effect on labour, delivery or subsequent neonatal progress. Ranitidine is also excreted in human breast milk. Like other drugs, Ranitidine should only be used during pregnancy or lactation if considered essential by a physician.

#### **Interactions with other medicinal products and other forms of interaction**

Ranitidine, at blood levels produced by standard doses, does not inhibit or interact significantly with the hepatic cytochrome P450-linked mixed function oxygenase system. Accordingly, ranitidine in usual therapeutic doses does not potentiate the actions of drugs such as diazepam, lidocaine, phenytoin, propranolol, theophylline and warfarin that are inactivated by this enzyme. To date interactions of ranitidine have not been shown with warfarin, barbiturates or diazepam.

#### **Pharmaceutical Information**

**Excipients:** Sodium chloride, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, dihydrate, Water for injections.

**Incompatibilities:** None known

**Shelf-life:** 2 years

**Storage Precautions:** Do not store above 25°C. Keep ampoules in the outer carton to protect from light.

**Nature of Container:** 2 ml solution in amber, type 1 glass ampoules.

**Instructions for Use and Handling:** Please refer to 'Dosage and method of administration'.

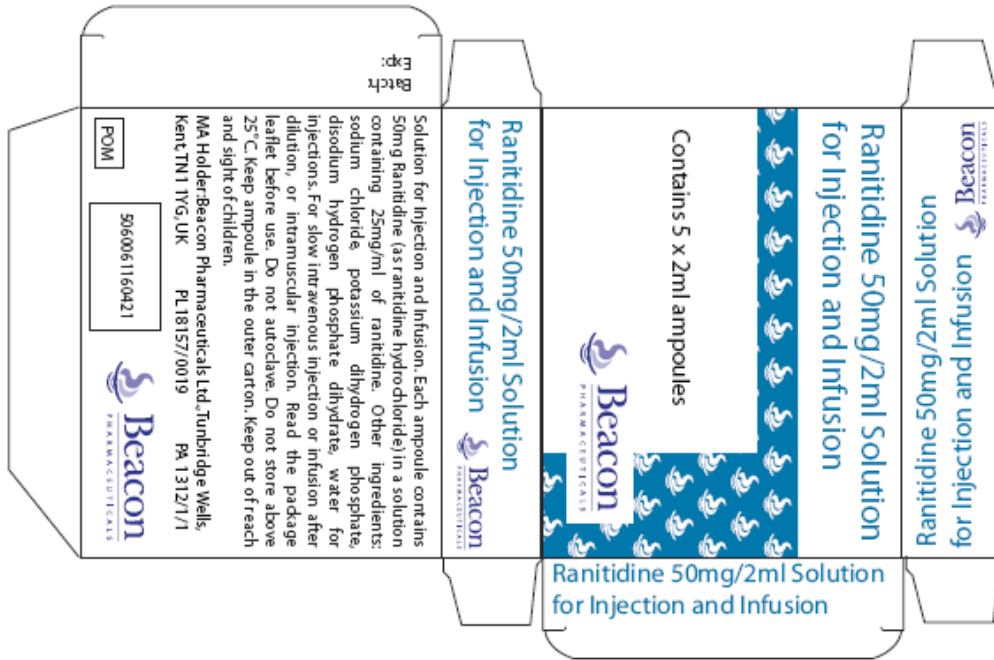
**Last revision:** January 2006



# Module 4

## Labelling

Dimensions: 90 x 74 x 20 mm



Ranitidine 50mg/2ml  
Injection and Infusion  
2ml ampoule  
For intravenous and  
intramuscular use  
Exp: BN:

## Module 5

### Scientific discussion during initial procedure

#### RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for ranitidine solution for injection and infusion, in the treatment of duodenal ulcers, benign gastric ulcers, reflux oesophagitis and associated conditions (See SPC) is approvable.

#### EXECUTIVE SUMMARY

##### Problem statement

This is an abridged application for marketing authorisation of ranitidine solution for injection and infusion via the decentralised procedure. The UK is the Reference Member State. The first UK marketing authorisation of ranitidine powder for solution for injection and infusion was granted in August 1993.

The Concerned Member State (CMS) is Ireland.

##### About the product

Ranitidine is one of histamine H<sub>2</sub>-receptor antagonists used for the treatment and prevention of relapse of peptic ulceration and the associated disease conditions. It is a specific rapidly acting histamine H<sub>2</sub>-antagonist. Ranitidine inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

##### General Comments on the submitted dossier

The application is in accordance with Article 10.1 Directive 2001/83EC. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product.

No Risk Management Plan other than documentation of pharmacovigilance system has been provided. For generics this is acceptable, since the innovator product is not subject to specific risk management measures.

User Consultation: PIL USER acceptance was submitted in December 2006. It is acceptable.



## **General Comments on Compliance with GMP, GLC, GCP and agreed ethical principles**

The RMS has been assured that acceptable standards of GMP are in place for these products type at all sites responsible for the manufacture and assembly of this product.

No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

## **SCIENTIFIC OVERVIEW AND DISCUSSION**

### **Quality aspects**

#### **Drug substance**

Active used to make the product has a Certificate of Suitability.

#### **Drug Product**

##### **Other Ingredients**

The other ingredients in the drug product are potassium phosphate monobasic, sodium phosphate dibasic dehydrate, sodium chloride and water for injection. The excipients are controlled by the Ph.Eur.

The product has been made at a licensed site. It is sterilised by filtration. Validation data on batches have been supplied. Sterilisation by aseptic processing is considered a non-standard process. Satisfactory validation is provided. Results of broth trials demonstrate that the process does not introduce microbial contamination.

There is a BP monograph for ranitidine injection. The specification complies with the BP monograph but different methods for assay and related substances are employed. The precautions for storage suggested are similar to the innovator.

The container is a Type I glass ampoule which is standard for a parenteral preparation. Satisfactory stability data has been provided justifying the shelf life of 2 years with the following storage conditions, "Keep container in the outer carton, do not store above 25°C, protect from light."

##### **Non clinical aspects**

Specific non-clinical studies have not been performed, as the application is submitted in accordance with Article 10.1 of Directive 2001/83/EEC as amended. The non-clinical overview gives an adequate update on the known pharmacological and toxicological properties of ranitidine hydrochloride.

## Clinical aspects

### Clinical Pharmacology

The product is a generic medicinal product as defined by article 10.1 of Directive 2001/83/EC, with the reference product being *Zantac*® Injection 50 mg/ 2ml ampoule by GlaxoSmithKline. Ranitidine solution 50 mg/ 2ml for injection and infusion is considered a generic of the reference medicinal product of *Zantac*® Injection 50 mg/ 2ml already marketed in many EU countries including the UK. It satisfies the criteria of having the same quantitative and qualitative composition with regards to active ingredients with the same pharmaceutical form. It is therefore considered bioequivalent with the reference product and that no bioequivalence study is required for this application.

### Clinical Efficacy & Safety

No new efficacy data are presented for this application and none are required. However, the applicant has provided an extensive review of clinical trials published in the literature confirming the efficacy and safety of ranitidine in the treatment and prevention of relapse of peptic ulceration and the associated disease conditions. No new safety issues have been identified.

### Summary of Product Characteristics, Patient Information Leaflet and Labels.

The SPC, PIL and labels were satisfactory.

### Risk/Benefit Assessment

H<sub>2</sub>-histamine receptor antagonists, including ranitidine, have been used for the treatment and prevention of relapse of peptic ulceration and the associated conditions for much more than ten years within the EU. The use of ranitidine is well established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted which include adequate review of published clinical data. When used as indicated, ranitidine has a favourable benefit-to-risk ratio. The hazard associated with ranitidine appears to be low and acceptable when considered in relation to its therapeutic benefit.

Marketing authorisation may therefore be granted.

## **Module 6**

### **Steps taken after procedure**

There have been no non-confidential alterations to the Marketing Authorisation.