

**RANZAC 75-P TABLETS
PL 19348/0125**

UKPAR

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**RANZAC 75-P TABLETS
PL 19348/0125**

LAY SUMMARY

The MHRA granted LPC Medical (UK) Ltd a Marketing Authorisation (licence) for the medicinal product Ranzac 75-P Tablets (PL 19348/0125). This product is available on the general sales list (GSL) for the treatment of symptoms of heartburn, indigestion, acid indigestion and hyperacidity.

Ranzac 75-P Tablets contain the active ingredient ranitidine which is an H₂- antagonist (anti-ulcer medication).

This application is a duplicate of a previously granted application for Ranzac 75mg Tablets (PL 19348/0110) and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ranzac 75-P Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

**RANZAC 75-P TABLETS
PL 19348/0125**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Ranzac 75-P Tablets (PL 19348/0125) to LPC Medical (UK) Ltd on 29 November 2007. The product is on the general sales list.

The application was submitted as simple abridged application according to article 10c of Directive 2001/83/EC as amended, cross-referring to Ranzac 75mg Tablets (PL 19348/0110), approved on 02 February 2005.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product. Since the cross-reference product was granted prior to the introduction of current legislation, no public assessment report (PAR) was generated for it.

The product contains the active ingredient ranitidine, as ranitidine hydrochloride, and is indicated for the short term symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity. Ranzac 75-P Tablets are also indicated for the prevention of acid indigestion, indigestion, hyperacidity and heartburn associated with consuming food and drink.

Ranitidine is an H₂-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a film-coated tablet containing the active pharmaceutical ingredient ranitidine, as ranitidine hydrochloride, at a strength of 75mg. The excipients present are microcrystalline cellulose, povidone, magnesium stearate and titanium dioxide E171. In addition, hypromellose, titanium dioxide E171, talc, macrogol 6000 and methacrylic acid copolymer are present in the film coating.

The tablets are presented in aluminium-foil blisters, in packs of 5, 6, 10 and 12 tablets.

DRUG SUBSTANCE

Ranitidine

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the Ph Eur specification is provided for ranitidine.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Ranitidine is stored in appropriate packaging.

Stability data have been generated supporting the proposed retest period when stored in the approved packaging.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory process validation has been carried out.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification.

Container Closure System

Satisfactory specifications and certificates of analysis have been provided for the packaging components.

Stability

Finished product stability data support the proposed shelf-life of 36 months with storage conditions 'Do not store above 25°C. Store in the original package'.

Bioequivalence/bioavailability

No bioequivalence study is required in support of this application.

SPC, PIL and Labels

The SPC and labels are pharmaceutically acceptable.

A patient information leaflet (PIL) has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION

It is recommended that a Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for an application of this type.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

The important quality characteristics of Ranzac 75-P Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new clinical data were submitted and none are required for applications of this type.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

**RANZAC 75-P TABLETS
PL 19348/0125**

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Marketing Authorisation application on 29 July 2005.
- 2 Following standard checks and communication with the applicant, the MHRA considered the application valid on 22 September 2005.
- 3 Following assessment of the application, the MHRA requested further information relating to the quality dossier on 11 October 2005, 24 January 2006, 07 July 2006, 12 July 2006, 23 August 2006, 05 September 2006 and 29 September 2006.
- 4 The applicant responded to the MHRA's requests, providing further information on 09 January 2006, 05 June 2006, 12 July 2006, 22 August 2006, 29 August 2006, 29 September 2006 and 21 May 2007 relating to the quality sections.
- 5 The application was determined on 29 November 2007.

**RANZAC 75-P TABLETS
PL 19348/0125**

STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ranzac 75-P Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75mg Ranitidine (as hydrochloride)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round biconvex film coated tablets with a break line on one side and the imprint "R75" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ranzac 75-P Tablets are indicated for the short term symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity.

Ranzac 75-P Tablets are also indicated for prevention of acid indigestion, indigestion, hyperacidity and heartburn associated with consuming food and drink.

4.2 Posology and method of administration

Dose

Adults (including the elderly) and children 16 years of age and above:

One Ranzac 75-P Tablet should be taken as soon as symptoms appear. If symptoms persist for more than one hour, or return a second Ranzac 75-P Tablet should be taken.

The maximum daily dose is four Ranzac 75-P Tablets.

For prevention of acid indigestion, indigestion, hyperacidity and heartburn associated with consuming food and drink, swallow one tablet with water, half to one hour beforehand.

Children:

Ranzac 75-P Tablets should not be taken by children under the age of 16 years.

Length of Treatment

Do not take the tablets for more than 14 days without the advice of a pharmacist or doctor.

Medical attention should be sought if symptoms worsen.

Method of administration

Ranzac 75-P Tablets should be swallowed whole with fluid.

4.3 Contraindications

Ranzac 75-P Tablets should not be given to patients known to have hypersensitivity to ranitidine or any component of the tablet.

Ranzac 75-P Tablets should not be given to children under 16 years because safety and efficacy have not been established in this patient group.

4.4 Special warnings and precautions for use

Ranitidine is excreted via the kidneys and so plasma levels of the drug are increased in patients with severe renal impairment. Ranzac 75-P Tablets are not suitable for these patients.

Patients taking non-steroidal anti-inflammatory drugs, especially the elderly, should seek their doctor's advice before using this product. Current evidence shows that ranitidine protects against NSAID associated ulceration in the duodenum and not in the stomach.

Treatment with a histamine H₂-antagonist such as Ranzac 75-P Tablets may mask symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition.

Administration of ranitidine to patients with a history of acute porphyria should, be avoided.

Patients should consult their doctor before taking Ranzac 75-P Tablets if:

- the patient has renal and / or hepatic impairment and under regular medical supervision for other reasons.
- the patient is suffering from any other illness or taking medications either physician prescribed or self prescribed.
- the patient has unintended weight loss in association with symptoms of indigestion.

- the patient is middle-aged or elderly with new or recently changed symptoms of indigestion.

4.5 Interaction with other medicinal products and other forms of interaction

At normal therapeutic dose, ranitidine does not inhibit hepatic Cytochrome P450-linked mixed function oxygenase system; although some minor interactions have been seen with some products these have not been shown to be of clinical relevance.

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

4.6 Pregnancy and lactation

Pregnancy:

Ranitidine crosses the placenta but therapeutic doses administered to obstetric patients in labour or undergoing caesarean section have been without an adverse effect on labour, delivery or subsequent neonatal progress. Like other medicines, ranitidine should only be used during pregnancy if absolutely necessary following appropriate medical consultation.

Lactation:

Ranitidine is found in human breast milk so nursing mothers should speak to their doctors before taking ranitidine.

4.7 Effects on ability to drive and use machines

No known effect.

4.8 Undesirable effects

Ranitidine is well tolerated although as with all drugs, some patients occasionally experience side effects. Listed below are side effects which have been reported for ranitidine. These have not necessarily occurred after taking 75mg ranitidine and could have occurred after taking 150mg and 300mg ranitidine.

Frequency estimate: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$); not known (cannot be estimated from the available data)

Cardiac disorders

Very rare: Arrhythmia, such as tachycardia or bradycardia, A-V conduction disturbance

Blood and lymphatic system disorders

Very rare: Leucopenia, thrombocytopenia, agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplastic anaemia. These effects are usually reversible.

Nervous system disorders

Rare: Headache, dizziness

Very rare: Severe headache and involuntary movement disorders. These have been reported mainly in elderly or severely ill patients.

Gastrointestinal disorders

Very rare: diarrhoea, acute pancreatitis

Renal and urinary disorders

Very rare: Acute interstitial nephritis

Skin and subcutaneous tissue disorders (see also Hypersensitivity)

Rare: Skin rash

Very rare: Erythema multiforme, alopecia

Musculoskeletal and connective tissue disorders

Very rare: Musculoskeletal symptoms such as arthralgia, myalgia

Vascular disorders

Very rare: vasculitis

Immune system disorders

Rare: Hypersensitivity reactions, including urticaria, fever, hypotension, angioneurotic oedema, bronchospasm, chest pain

Very rare: Anaphylactic shock.

Hepatobiliary disorders

Rare: Transient and reversible changes in liver function test values

Very rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) and with or without jaundice. These were usually reversible.

Reproductive system and breast disorders

Very rare: Gynaecomastia, erectile dysfunction

Psychiatric disorders

Very rare: confusion, hallucinations and depression. These have been reported mainly in elderly or severely ill patients.

4.9 Overdose

Complications from overdose are not expected after oral administration.

Treatment for overdose:

Haemodialysis can be used to remove drug from the plasma.

Symptomatic and supportive treatment should be given as required.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC code: A02BA02

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 long duration of action and a single 75mg dose suppresses gastric acid secretion for up to twelve hours. Clinical studies have shown that ranitidine 75mg can relieve the symptoms of excess acid production for up to twelve hours.

5.2 Pharmacokinetic properties

Ranitidine is rapidly absorbed after oral administration with mean peak levels occurring at 2 to 3 hours. Bioavailability of ranitidine tablets is 50% on average.

In the liver ranitidine is metabolised to ranitidine-N-oxide, N-desmethyranitidine, ranitidine-S-oxide and a furan acid analogue. About 35% of the orally administered dose is excreted unchanged in the urine within 24 hours, 6% of the dose is excreted as the N-oxide, 2% as the S-oxide, 2% as desmethyl ranitidine and 1-2% as the furoic acid analogue.

In persons with normal renal functions the elimination half-life after oral administration is 2 to 3 hours.

Absorption is not significantly impaired by food and antacids. Ranitidine is not extensively metabolised. Elimination of the drug is primarily by tubular secretion. The elimination half-life of ranitidine is 2-3 hours.

5.3 Preclinical safety data

Ranitidine has a high safety margin. 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 gastro acid secretion. Rapid respiration and muscular tremors with one fatality occurred in dogs receiving 450mg/kg ranitidine. Rats tolerated daily doses of 2,000mg/kg for 78 weeks well.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline Cellulose

Povidone

Magnesium Stearate

Titanium Dioxide (E171)

Coat

Hypromellose

Titanium dioxide (E171)

Talc

Macrogol 6000

Methacrylic acid copolymer.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in the original pack. Do not store above 25°C.

6.5 Nature and contents of container

Blister strips of 5 or 6 tablets comprising aluminium foil on both sides.

The strips are packed in cartons to contain 5, 6, 10 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

LPC Medical (UK) Ltd

30 Chaul End Lane

Luton, Bedfordshire

LU4 8EZ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 19348/0125

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/11/2007

10 DATE OF REVISION OF THE TEXT

29/11/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

RANZAC 75-P TABLETS

(Ranitidine 75mg tablets)

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However, you still need to take Ranzac 75-P Tablets carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- 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 pharmacist.

In this leaflet:

1. What Ranzac 75-P Tablets are and what they are used for
2. Before you take Ranzac 75-P Tablets
3. How to take Ranzac 75-P Tablets
4. Possible side effects
5. How to store Ranzac 75-P Tablets
6. Further information

1. WHAT RANZAC 75-P TABLETS ARE AND WHAT THEY ARE USED FOR

The name of your medicine is Ranzac 75-P Tablets. It contains the active ingredient called Ranitidine Hydrochloride.

Ranitidine belongs to a group of medicines called H₂-antagonists. It works by preventing your stomach from producing too much acid and its effects last for up to 12 hours.

The tablets are used to relieve the burning sensation in the stomach and chest caused by heartburn, indigestion, acid indigestion and hyperacidity (too much acid).

2. BEFORE YOU TAKE RANZAC 75-P TABLETS

Do not take Ranzac 75-P Tablets if you have an allergy to Ranitidine or to any of the ingredients listed at the end of this leaflet.

If you are not sure whether you should start taking Ranzac 75-P Tablets, talk to your doctor.

Ranzac 75-P Tablets is not recommended for children under 16 years old.

You must tell your doctor or pharmacist if you :

- have been told by a doctor that you have an ulcer in the stomach or small intestine (lower part of your stomach)

- have kidney and/or liver problems
- are under regular medical supervision for other reasons
- are suffering from any other illness or taking medications either prescribed by a physician or prescribed by yourself
- have lost weight unintentionally linked with symptoms of indigestion
- are middle-aged or elderly with new or recently changed symptoms of indigestion
- are taking non-steroidal anti-inflammatory painkillers (NSAIDs, such as Aspirin)
- have the rare condition called porphyria
- are pregnant, or intend to become pregnant
- are breast-feeding or intend to breast-feed

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

3. HOW TO TAKE RANZAC 75-P TABLETS

Swallow one tablet (75 mg of Ranitidine) whole with water as soon as symptoms appear.

If symptoms are not controlled or return within one hour, swallow another tablet.

For prevention of heartburn associated with consuming food and drink, indigestion, acid indigestion and hyperacidity (too much acid), swallow one tablet with water, half to one hour beforehand.

Do not take more than four tablets (75 mg of Ranitidine) in 24 hours.

Medical attention should be sought if symptoms worsen. Do not take tablets for more than 14 days without the advice of a pharmacist or doctor.

If you forget to take Ranzac 75-P Tablets:

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to. Otherwise, take it as soon as you remember, and then go back to taking it as you would normally.

Do not take a double dose to make up for the dose that you missed.

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

If you take more Ranzac 75-P Tablets than you should:

Immediate medical advice should be sought in the event of taking too many tablets or an overdose, even if you feel well.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ranzac 75-P Tablets can cause side effects, although not everybody gets them.

You must stop taking the tablets and tell your doctor immediately, if your chest suddenly feels tight and you start to wheeze or get a skin rash or swelling of the face, lips, throat and eyelids.

Check with your doctor as soon as possible if any of these side effects are noticed:

Rare

- Headache
- Dizziness
- Changes to blood counts (causing tiredness, bruising, fever or frequent infections)
- Diarrhoea
- Nausea
- Muscle and joint pains
- Jaundice or yellowing of the skin
- Abnormally low blood pressure
- Acute pancreatitis (inflammation of the pancreas, which causes severe pain in the abdomen and back)
- Highly or excessively sensitive reactions like an itchy skin eruption
- Rare cases of hepatitis, with or without jaundice (which are usually reversible)

Very rare

- Visual disturbances
- Changes in heart rate (faster or slower)

- Vasculitis (inflammation of blood vessels) or a rash related to vasculitis, inflammation of the kidney which can cause swollen ankles or high blood pressure
- Breast enlargement
- Erectile dysfunction (impotence) in men
- Severe headache, confusion, hallucinations or depression (mainly in elderly or severely ill patients)

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 pharmacist.

5. HOW TO STORE RANZAC 75-P TABLETS

Keep out of the reach and sight of children.

Store in the original pack. Do not store above 25°C.

Do not take Ranzac 75-P Tablets after the expiry date (EXP) printed on the pack. The expiry date refers to the last day of that month.

If you have any Ranzac 75-P Tablets left, return them to your pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What is in Ranzac 75-P Tablets?

Each tablet contains 75mg Ranitidine as Ranitidine Hydrochloride.

The tablet also contains Microcrystalline Cellulose, Povidone, Magnesium Stearate, Hypromellose, Talc, Macrogol 6000, Methacrylic acid copolymer and the colouring agent E171.

Ranzac 75-P Tablets are white to off-white, round biconvex film coated tablets with a break line on one side and the imprint "R75" on the other side.

The carton contains 5 (6, 10 or 12 as appropriate) tablets.

Marketing Authorisation Holder and Manufacturer:

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LABELLING

