SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZARIDEX 150, tablets
ZARIDEX 300, caplets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZARIDEX 150 mg: Each tablet contains ranitidine 150 mg (as hydrochloride).
Excipients with known effect:
Each tablet contains approximately 4 mg lactose.
Each tablet contains approximately 1.1 mg sodium.

ZARIDEX 300 mg: Each caplet contains ranitidine 300 mg (as hydrochloride).
Excipients with known effect:
Each caplet contains approximately 7 mg lactose.
Each tablet contains approximately 2.2 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

150 mg tablet, 300 mg caplet.

ZARIDEX 150: Yellow, round, film-coated tablets.

ZARIDEX 300: Yellow, film-coated caplets scored on one side. The score line is not intended for breaking the caplet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
Zaridex is indicated for the treatment of duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents. Zaridex is also indicated for the treatment of post-operative ulcer, Zollinger-Ellison Syndrome and oesophageal reflux disease including long term management of healed oesophagitis. Zaridex is indicated for the following conditions where reduction of gastric secretion and acid output is desirable; the prophylaxis of gastro-intestinal haemorrhage from stress ulceration in seriously ill patients and before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's Syndrome), particularly obstetric patients during labour.

Children (6 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

Posology

Adults (including the elderly)

- The usual dosage is 150 mg twice daily, taken in the morning and evening.
- Alternatively, patients with duodenal ulceration, gastric ulceration or oesophageal reflux disease may be treated with a single bedtime dose of 300 mg. It is not necessary to time the dose in relation to meals.
- Duodenal ulcer, benign gastric ulcer and post-operative ulcer:
  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.
- NSAID associated peptic ulceration:
  In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, 8 weeks treatment may be necessary.
- In duodenal ulcer 300 mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ranitidine 150 mg twice daily or 300 mg nocte. The increased dose has not been associated with an increased incidence of unwanted effects.
- 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.
- 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 if necessary 12 weeks.
- Moderate to severe oesophagitis:
  In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg 4 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, recommended adult dose is 150 mg twice daily. Long term treatment is not indicated in 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 150 mg three times daily and this may be increased as necessary. Patients with this syndrome have been given increasing doses up to 6 g per day and these doses have been well tolerated.
- Prophylaxis of haemorrhage from stress ulceration:
  In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients, treatment with ZARIDEX 150 mg twice daily may be substituted for ranitidine injection once oral feeding commences in patients considered to be still at risk from this condition.

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

  In obstetric patients at commencement of labour, an oral dose of 150 mg may be given followed by 150 mg at six 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 (e.g. 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 6 to 11 years and over 30kg of weight:
  See section 5.2 Pharmacokinetic Properties (Other special populations).
- Patients over 50 years of age
  See section 5.2 Pharmacokinetic Properties (Other special populations).
- Peptic Ulcer Acute Treatment:
  The recommended oral dose for treatment of peptic ulcer in children is 4 mg/kg/day to 8 mg/kg/day administered as two divided doses to a maximum of 300 mg 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 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).
- Patients with 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.
- Method of administration
  For oral administration.

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

Malignancy
The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and in patients of middle age and over with new or recently changed dyspeptic symptoms) as treatment with ranitidine may mask symptoms of gastric carcinoma.

Renal Disease
Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. The dose should be adjusted as detailed in section 4.2 Patients with renal impairment.

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly. Current evidence shows that ranitidine protects against NSAID associated ulceration in the duodenum and not in the stomach.

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 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). 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).

- ZARIDEX contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- ZARIDEX contains the excipient sunset yellow FCF (E110), which may cause allergic reactions.

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, propanolol 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 level 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

Pregnancy
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. 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 breast-feeding if considered essential.

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).

4.7 Effects on ability to drive and use machines
None reported.

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). 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. 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.

Not known: 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.

Vascular Disorders

Very Rare: Vasculitis.

Gastrointestinal Disorders

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

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

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

Very Rare: Acute interstitial nephritis.

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 assessed in children ages 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 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Symptoms and signs

Ranitidine is very specific in action and accordingly no particular problems are expected following overdosage.

Treatment

Symptomatic and supportive therapy should be given as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

- Pharmacotherapeutic group: H2-receptor antagonists
- ATC code: A02BA02.
- **Mechanism of action**

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.

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 a 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.

Other special populations:

- Children (6 years and above):
  Limited pharmacokinetic data have shown that there are no significant differences in half-life (range for children 6 years and above: 1.7 - 2.2 h) and plasma clearance (range for children 6 years and above: 9 - 22 ml/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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Croscarmellose sodium, Lactose monohydrate, Magnesium stearate, Hypromellose, Basic butylated methacrylate copolymer, Quinoline yellow Al Lake (E104), Triacetin, Titanium dioxide (E171), Iron oxide yellow (E172), Sunset yellow FCF Al lake (E110), Carnauba wax.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister.
Pack sizes: 10, 20, 30 or 100 tablets/caplets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Dexcel Ltd. 1 Dexcel Street, Or Akiva 3060000, Israel.

8. MARKETING AUTHORISATION HOLDER

Dexcel Ltd. 1 Dexcel Street, Or Akiva 3060000, Israel.

9. LICENSE NUMBER

<u>Zaridex 150</u>

109-28-29272-00

<u>Zaridex 300</u>

109-45-29273-00

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