CPMP/835/95

FINAL OPINION OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS IN ACCORDANCE WITH ARTICLE 12 OF DIRECTIVE 75/319/EEC AS AMENDED

Name of product:	ZAGAM
International non-proprietary name (INN):	Sparfloxacin
Strength:	200mg
Pharmaceutical form:	White film coated tablets
Route of administration:	Oral administration

Basis for Opinion

On June 6, 1995 Denmark presented a referral under Article 12 of Council Directive 75/319/EEC as amended, and asked the CPMP to formulate an opinion on risks and benefits of ZAGAM 200 mg (Sparfloxacin) tablets. The ground for referral was a Rapid Alert dated May 31, 1995 from France informing of 643 case reports over a period of 7 months, 80% of which concern phototoxicity (letter from Denmark appended).

The initial time frame agreed on June 6, 1995 by the CPMP was 90 days, extended to an extra period of 90 days on September 12, 1995.

A consolidated list of questions was sent to the Marketing Authorisation Holders on July 18, 1995. Written explanation was provided by the Marketing Authorisation Holders on August 21, 1995. Additional information was provided by the Marketing Authorisation Holders on September 21, 1995 and November 17, 1995.

Opinion

The Committee, having considered the matter on *December 19, 1995* is of the opinion that the marketing authorisations for ZAGAM 200 mg (Sparfloxacin) should be maintained provided that:

- the Summary of Product Characteristics is amended as stated in Annex I

- provision of further evaluation is given as laid down in Annex II

The present opinion is forwarded to the Commission, to Member States and to the marketing authorisation holders together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions together with its annexes and appendices.

London, *19 December 1995*

Prof. J M Alexandre
Chairman, on behalf of the CPMP

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

(Article 4a of Directive 65/65/EEC as amended)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME of the MEDICINAL PRODUCT

ZAGAM (sparfloxacin) 200 mg

2. QUALITATIVE and QUANTITATIVE COMPOSITION

Sparfloxacin 200 mg

3. PHARMACEUTICAL FORM

White film-coated tablets for oral use. The tablets are marked on one face with RPR201.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Because of its severe adverse reaction profile, sparfloxacin use must be restricted to treatment of radiologically confirmed community acquired pneumonia which has failed to respond to conventional therapy:

- either caused by pneumococci, highly resistant to penicillin (MIC ≥ 2 mg/l) and other antimicrobials,
- or occurring in an epidemiological environment indicating that the risk of such a multiresistant strain is high.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

This medication can be taken with or without food, preferably in the evening.

In patients with normal renal function:

- 400 mg as a single dose on the first day,
- then 200 mg/day in a single daily dose.

The duration of maintenance therapy is 10 days on average, to a maximum of 14 days.

No benefit is to be expected by increasing the daily dose.

In patients with renal failure:

- No studies have been performed in patients with moderate renal impairment (creatinine clearance ≥ 30 ml/min). Due to the small rate of urinary elimination (≈ 10 %) no dosage adaptation is necessary. Nevertheless, caution should be observed in this group of patients.
- In severe renal failure (creatinine clearance < 30 ml/min), the following dosage schedule should be observed:

- 400 mg loading dose the first day
- then 200 mg the third day
- then every 48 hours, for a maximum of 14 days.

- Safe administration in haemodialysis or peritoneal dialysis patients has not been established. Therefore administration of sparfloxacin to these patients is not recommended.

In patients with hepatic failure

- Hepatic impairement without cholestasis : no dosage modification is required (see "Pharmacokinetic properties")

- No data are available on patients with serious hepatic insufficiency.

4.3. CONTRA-INDICATIONS

- Exposure to the sun, bright natural light and UV rays (see “Special Warnings and Special precautions for use”): it is essential to avoid exposure to the sun, bright natural light and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped.

- Hypersensitivity to sparfloxacin or to drugs in the quinolone family.

- Concomitant use with amiodarone, sotalol and bepridil (see “Interaction with other medicinal products and other forms of interaction”).

- In pregnant or lactating women (see “Pregnancy and lactation”).

- In children until the end of the growth phase.

- History of tendon disease with a fluoroquinolone.

- Glucose-6-phosphate dehydrogenase deficiency.

- Known Q-T interval prolongation (congenital or acquired)

Concomitant use of antiarrhythmic agents or other drugs which produce torsades de pointes (see "Interaction with other medicinal products and other forms of interaction").

4.4.SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Phototoxicity:

Phototoxic reactions are common and are characterized by redness, swelling and blisters. These reactions are sometimes severe, patients may develop second degree burns and may require hospitalisation. The frequency of these reactions is higher than with other fluoroquinolones.

Phototoxicity can occur in cloudy weather or even in the absence of direct exposure to the sun.

Consequently, patients should be advised to avoid exposure to the sun, bright light and UV rays throughout the entire duration of treatment and for 5 days after treatment is stopped.

Patients must be instructed to discontinue sparfloxacin therapy at the first sign or symptom of phototoxicity and to avoid further exposure to the sun, bright light or UV rays for the next 5 days.

Recovery from phototoxicity may be slow and recurrence may occur even several weeks after withdrawal of sparfloxacin.

Increase in the Q-T interval:

Increases in the Q-Tc interval have been observed in healthy volunteers treated with sparfloxacin, a mean maximum increase of 19 msecs was observed at the recommended dosage of 400/200 mg. In clinical trials involving 813 patients, the average prolongation was around 3%, and 1.2% of patients developed Q-Tc intervals greater than 500 msec (prolongation of 100 msecs in 0.3%), but with no arrhythmic effects.

As a consequence, the use of sparfloxacin in patients with known Q-Tc prolongation congenital or acquired (e.g. acute myocardial infarction) and the concomitant use of drugs known to produce an increase in the Q-Tc interval and/or torsades de pointes is inadvisable : e.g. quinine, chloroquine, erythromycin, terfenadine, astemizole, probucol, halofantrine, pentamidine, vincamine, class Ia antiarrhythmic agents (e.g. quinidine, procainamide, disopyramide), class III anti-arrhythmic agents (e.g. bretylium), some tricyclic antidepressants, some neuroleptics (e.g. sultopride, phenothiazines) (see “Interaction with other medicinal products and other forms of interaction”).

Sparfloxacin is contra-indicated in patients receiving amiodarone, sotalol or bepridil (see “Contra-indications”).

Conditions that predispose to the development of torsades de pointes:

- Hypokaliemia: patients with a known history of hypokaliemia including that caused by concomitant medications (see "Interaction with other medicinal products and other forms of interaction") should have their potassium concentrations corrected before commencing treatment with sparfloxacin.

- Bradycardia of any cause

- Atrio-ventricular conduction defects

- Use with caution and under close surveillance in case of cardiac arrhythmias in particular in case of bradyarrhythmias.

Tendinitis:

Tendinitis and/or tendon rupture (particularly affecting the Achilles tendon) occurs in association with quinolone antibiotics. Such reactions have particularly been noted in older patients and those on corticosteroids. At the first sign of pain or inflammation, patients should discontinue sparfloxacin and rest the affected limb. If symptoms involve the Achilles tendon,

measures should be taken to ensure that rupture of both does not occur (e.g. both are supported with a suitable brace or heelpiece).

Mycobacteria:

In cases of suspected tuberculosis, the potential activity of sparfloxacin against mycobacteria should be taken into account. Sparfloxacin may produce false-negative culture results for mycobacteria.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Contra-indicated concomitant medications:

- Amiodarone, sotalol and bepridil: risk of torsades de pointes due to prolongation of the Q-T interval (additive electrophysiologic effects).

Inadvisable concomitant medications:

- Drugs that produce QT prolongation and/or torsades de pointes:

  . antiarrhythmic agents: bretylium, disopyramide, procaïnamide, quinidine.

  . other drugs : astemizole, erythromycin, quinine, chloroquine, halofantrine, pentamidine, probucol, terfenadine, vincamine, some tricyclic antidepressants, some neuroleptics (e.g. sultopride, phenothiazines) : risk of torsades de pointes due to prolongation of the Q-Tc interval (additive electrophysiologic effects). Close clinical and electrocardiographic monitoring is required if it is considered essential to use with any of these drugs.

Concomitant medications requiring precautions for use:

- Iron salts (oral use): reduction of the bioavailability of sparfloxacin due to chelation and due to a nonspecific effect on the absorption capacity of the gastrointestinal tract. Iron salts should be taken after sparfloxacin (at least 2 hours later if possible).

- Salts, oxides and hydroxides of magnesium, aluminium and calcium (antacids) : reduction of the gastrointestinal absorption of sparfloxacin. Antacids should not be taken at the same time as sparfloxacin (at least 4 hours apart if possible).

- Zinc salts (oral use), described for zinc salts at doses > 30 mg/d : reduction of the gastrointestinal absorption of sparfloxacin. Zinc salts should be taken after sparfloxacin (at least 2 hours later if possible).

- Hypokaliemia cause by drugs such as non-potassium sparing diuretics, stimulant laxatives, amphotericin B (IV.),cortico-steroids and tetracosacaride may pre-dispose to the development of torsades de pointes. Potassium levels should be within the normal range before treatment with sparfloxacin is started. Hypokaliemia should not be allowed to develop during sparfloxacin use.

- Bradycardia caused by drugs such as digoxin and beta-blockers may predispose to the development of torsades de pointes. If it is considered essential that sparfloxacin is used in conjunction with therapy associated with bradycardia, then close electrocardiographic monitoring should be carried out.

Concomitant medications to be taken into account

- NSAIDs and theophylline: quinolone antibiotics can reduce the seizure threshold particularly in association with drugs such as NSAIDs and theophylline.

4.6. PREGNANCY AND LACTATION

There are no human studies of the use of sparfloxacin in pregnancy and lactation. However, reproduction studies performed in rats, rabbits and monkeys dosed orally did not reveal any evidence of impairment of fertility and peri/post natal development. When administered to rats during organogenesis, sparfloxacin demonstrates a dose-related increase in the incidence of ventricular septal defects (this effect was not observed in primate studies). In common with other quinolones, sparfloxacin has demonstrated arthrotoxic potential in growing animals. Women of childbearing potential should be advised to avoid becoming pregnant during sparfloxacin therapy and sparfloxacin should not be prescribed to pregnant women.

Sparfloxacin is secreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended that women be advised not to breast feed during sparfloxacin therapy.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about the potential for central nervous system effects, and advised not to drive or operate machinery whilst taking sparfloxacin.

4.8. UNDESIRABLE EFFECTS

- **Phototoxicity** including manifestations of sunburn, erythema and severe bullous lesions. Recurrence of the symptoms after a new sun exposure, several weeks after the end of the treatment, has been sometimes observed.

- **Skin reactions**: rash, pruritus, swelling, blisters.

- **Musculoskeletal**: muscle or joint pain, tendinitis, ruptured tendon (see "Contra-indications" and "Special Warnings and Special Precautions for use").

- **Cardiovascular**: rare cardiac rhythm disorders including torsades de pointes, arrhythmia, bradycardia, tachycardia and ventricular tachycardia (see "Contraindications" and "Interaction with other medicinal products and other forms of interaction").

- **Digestive disorders**: nausea, vomiting, diarrhoea, abdominal pain, gastralgia.

- **Nervous System**: tremor, feeling drunk, paresthesia, sensory disturbance, headache and vertigo.

- **Psychiatric disorders**: hallucinations, sleep disorders at the beginning of treatment.

- **Body as a whole**: rare cases of hypersensitivity, including urticaria, angioedema, anaphylactic shock and Quincke's oedema.

- **Hematologic System**: isolated cases of thrombocytopenia and rare cases of thrombocytopenic purpura.

- **Vision disorders**: Conjunctivitis and uveitis.

4.9. OVERDOSE

In case of overdose, the patient should be monitored in a suitably equipped unit and advised to avoid sun exposure for 5 days. ECG monitoring is recommended due to the possible prolongation of the QTc interval. There is no known antidote for sparfloxacin overdosage.

5. PHARMACOLOGICAL PROPERTIES

ANTIBIOTIC FROM THE QUINOLONE FAMILY
(J : Anti-infectious)

5.1. PHARMACODYNAMIC PROPERTIES

Sparfloxacin, an aminodifluoroquinolone, is a synthetic antibiotic belonging to the quinolone family. Sparfloxacin exhibits a spectrum of activity which is related to the therapeutic indication described in chapter 4.1 and focused on *S.pneumoniae*.
However, other bacterial species usually susceptible to sparfloxacin can be associated in community acquired pneumonia. In such a situation, no combination therapy is needed because of a spectrum of activity which includes all respiratory pathogens.

- Susceptible species (MIC ≤ 1 mg/l) :

Streptococcus pneumoniae including those strains resistant to beta-lactam and macrolide antibiotics
Streptococcus of groups A, C and G
Methicillin-susceptible *Staphylococcus*
Haemophilus influenzae including beta-lactamase producing strains
Moraxella catarrhalis
Mycoplasma pneumoniae, Chlamydia psittaci and pneumoniae
Legionella

- Resistant species (MIC > 2 mg/l) :

Methicillin-resistant *Staphylococcus*

5.2. PHARMACOKINETIC PROPERTIES

Absorption:

The absorption of sparfloxacin is rapid with peak serum concentrations achieved 3 to 5 hours after the first dose. Oral absorption is not modified by the presence of food. Steady-state plasma concentrations are achieved on the first day due to the loading dose that is double the daily dose.

Dosing regimen	Day 1		Steady state	
	Cmax mg/ml	Cmin mg/ml	Cmax mg/ml	Cmin mg/ml
400 mg*/200 mg**	1.7	0.6	1.4	0.5

* Loading dose
** Daily dose

Distribution:

After a loading dose of 400 mg, the concentrations found in the extravascular fluid are equivalent to plasma concentrations. In bronchopulmonary tissues, concentrations reached are greater than the MIC of the bacterial species susceptible to sparfloxacin: 10 mg/g in pulmonary parenchyma, 16.7 mg/ml in alveolar surfactant and 2-5 mg/g in bronchial mucosa.

Sparfloxacin concentrates preferentially in macrophages, in which concentrations of 40-50 mg/g are reached.

Plasma protein binding is 45 %.

Metabolism:

Sparfloxacin is metabolized in the liver to an inactive glucuronide conjugate. Metabolism does not depend on cytochrome mediated oxidation, in particular the cytochrome P450 system.

Elimination:

The terminal plasma elimination half-life is approximately 20 hours. Excretion is both fecal and urinary: two-thirds is excreted in the feces as unchanged sparfloxacin, one-third is eliminated in the urine as unchanged sparfloxacin and as the glucuronide conjugate.

Biliary excretion, mainly as the glucuronide conjugate, accounts for 10-20 % of the administered dose.

Special Populations:

Patients with renal impairment: In patients with renal impairment (creatinine clearance < 30 ml/min), the elimination half-life of sparfloxacin is 35-40 hours due to partial hydrolysis of the glucuronide conjugate. The accumulation of the glucuronide conjugate is observed in these patients.

Patients with hepatic impairment: The elimination half-life is unchanged in patients with hepatic impairment without cholestasis.

Elderly: The pharmacokinetic properties of sparfloxacin are not modified in the elderly.

5.3. PRECLINICAL SAFETY DATA

Sparfloxacin exhibits the toxicity profile as following :

- hepatotoxicity based on an increase in hepatic enzymes (e.g. aspartaminotransferase) and a cytologic alteration of the hepatocytes, notably vacuolisation and multifocal or single cell liver necrosis ;
- nephrotoxicity, notably glomerulo-nephritis and interstitial nephritis ;
- cardiotoxicity with a pronounced prolongation of the QT interval, occured already in doses close human dosage ;

- arthrotoxicity ;

- phototoxicity ;

Under simultaneous U.V. exposure, sparfloxacin can exhibit mutagenic properties and carcinogenetic effects.

Reproductive toxicity studies detected anomalies such as ventricular septum defect in young rats, but these effects were not observed in young monkeys.

6.PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Microcrystaline cellulose
Maize starch
L. Hydropropyl cellulose
Magnesium stearate
Anhydrous colloïdal silica
Methylhydroxypropyl cellulose
Polyethylen Glycol 6000
Titanium dioxide

6.2. INCOMPATIBILITIES

6.3. SHELF-LIFE

2 years.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

6.5. NATURE AND CONTENTS OF CONTAINER

Thermoformed blister pack (PVC-PE-PVDC)

6.6. INSTRUCTIONS FOR USE/HANDLING

6.7. PRESENTATIONS

6 tablets in a thermoformed blister pack (PVC-PE-PVDC)

6.8. MARKETING AUTHORISATION HOLDERS

RHÔNE D.P.C. EUROPE
20 avenue Raymond Aron
92165 Antony Cedex
FRANCE

SPECIA
16 rue Clisson
75636 Paris Cedex
FRANCE

RHONE-POULENC RORER
boulevard Sylvain Dupuis 243
Boite 3
1070 Brussels
BELGIUM

7. MARKETING AUTHORISATION NUMBER
8. DATE OF APPROVAL OF THE SPC

ANNEX II

SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDERS

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SPECIFIC OBLIGATIONS OF THE MARKETING AUTHORISATION HOLDERS

Given that no evidence is currently available to clarify Sparfloxacin's potential as a photomutagen or photocarcinogen, it was agreed by the CPMP that the findings of studies investigating photomutagenicity and photocarcinogenicity must be provided to the CPMP by the end of 1996 at the latest.

Given the risks associated with Sparfloxacin and the restricted indications accepted by the CPMP, it was agreed that six monthly updates on efficacy and safety must be provided to the CPMP for at least two years from the date of the opinion.