IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0876/003/001
Case No: 2038957

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

TAD Pharma GmbH

Heinz-Lohmann-Strasse 5, **D-27472 Cuxhaven**, **Germany**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Norflocux 400 mg film coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/01/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Norflocux 400 mg film coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg norfloxacin.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, round film-coated tablet with a break score on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of upper and lower, complicated and uncomplicated, acute and chronic urinary tract infections, if the infection is treatable by oral drug administration. These infections include cystitis, pyelitis, pyelonephritis, chronic prostatitis and those urinary tract infections associated with urological surgery, neurogenic bladder or nephrolithiasis caused by bacteria susceptible to norfloxacin.
Before prescribing norfloxacin, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

4.2 Posology and method of administration

Susceptability of the causative organism to norfloxacin should be tested.
However, therapy may be initiated before obtaining the results of the tests.

Diagnosis	Dosage	Duration of therapy
Uncomplicated lower urinary tract infections (e.g. cystitis)	400 mg norfloxacin (1 tablet) twice daily	3 days
Urinary tract infections[#]	400 mg norfloxacin (1 tablet) twice daily	7 - 10 days
Chronic relapsing urinary tract infections *	400 mg norfloxacin (1 tablet) twice daily	up to 12 weeks

[#] Symptoms of urinary tract infection may disappear after 1 or 2 days. Nevertheless, the recommended time of duration of treatment should be kept completely.

* If adequate suppression is obtained within the first four weeks of therapy, the dose of Norfloxacin may be reduced to 400 mg norfloxacin (1 tablet) daily.
Up to now, no data on a therapy lasting longer than eight weeks are available.

Patients with renal impairment:
Clinical studies showed that the mean plasma half life of norfloxacin was approximately 8 hours in patients whose creatinine clearance was less than
30ml/min; there was no difference in the mean half-life of norfloxacin in patients with a creatinine clearance of less than 10 ml/min, compared to patients with creatinine clearance of 10-30 ml/min. For these patients the recommended dose is 400 mg norfloxacin once daily.

Use in the elderly:
Pharmacokinetic studies have shown no appreciable changes, when compared to younger patients, apart from a slight prolongation of half-life. In the absence of renal impairment no adjustment of the dosage is necessary.

Children and growing adolescents:
Norfloxacin is not recommended for use in children or growing adolescents.

Method of administration:
Norfloxacin tablets should be taken with sufficient fluid (e.g. a glass of water) at least one hour before or two hours after a meal or ingestion of milk.
The film-coated tablet should preferably be taken in the morning and in the evening. In case of once-daily dosage, it should be taken at the same time of day.

4.3 Contraindications

Hypersensitivity to norfloxacin, to other quinolones or to any of the excipients of this product.
Norfloxacin is not recommended for use in children or growing adolescents.
Norfloxacin is contraindicated in patients with a history of tendinitis and/or tendon rupture related to fluoroquinolone administration (*see section 4.4, Special warnings and precautions for use and section 4.8, Undesirable effects*).
Norfloxacin is contraindicated during pregnancy and lactation.

4.4 Special warnings and precautions for use

Use in patients with epilepsy and other CNS disorders
Caution is advised in patients with a history of CNS disturbances like convulsions, epilepsy or other known factors that predispose to seizures.
Norfloxacin should not be used in these patients unless there is an overwhelming clinical need.

Hypersensitivity reactions
Norfloxacin can cause serious, potentially fatal hypersensitivity reactions (anaphylactic and anaphylactoid reactions), occasionally following the initial dose (*See section 4.8, Undesirable effects*). Patients should be advised to discontinue treatment immediately if experiencing such reactions and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Photosensitivity
During the treatment patients should avoid direct exposure to the sun and to other kinds of UV-light, like solarium. If hypersensitivity to light appears the treatment should be withdrawn.

Use in renal impairment
In patients with severe renal impairment, the risk/benefit ratio of using norfloxacin should be carefully weighed for the individual *see section 4.2***,** *Posology and method of administration*). The urinary concentration of norfloxacin may be reduced in patients with severely impaired renal function as norfloxacin is predominantly excreted via the kidneys.

Crystalluria
In case of prolonged treatment, the occurrence of crystalluria should be monitored. While crystalluria is not expected to occur under normal conditions with a dosage regimen of 400 mg twice daily, as a precaution, the daily recommended dosage should not be exceeded and the intake of sufficient fluids should be guaranteed to ensure a proper state of hydration and adequate urinary output.

Tendinitis and/or tendon rupture
Norfloxacin should not be used in patients with a present or past injury, inflammation or rupture of the Achilles tendon (*See section 4.3, Contraindications* and *section 4.8, Undesirable effects*)Tendinitis and/or tendon rupture (particularly the Achilles tendon) may occur with quinolone antibiotics. Such reactions have been observed, particularly in older patients and in those treated concurrently with corticosteroids. On the appearance of tendon pain or signs of inflammation of the Achilles tendon, treatment with norfloxacin must be discontinued immediately and the patient treated accordingly.

G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency
In patients with latent or actual G6PD-(Glucose-6-phosphate-dehydrogenase) deficiency quinolone class haemolytic reactions are possible.

Use in patients with myasthenia gravis
Norfloxacin can exacerbate the symptoms of myasthenia gravis which may result in life threatening weakness of respiratory muscles. Adequate countermeasures should be taken at any sign of respiratory distress.

Pseudomembranous colitis
The occurrence of severe and persistent diarrhoea during or after therapy may be an evidence for very rarely observed pseudomembranous colitis. In such cases therapy must be stopped immediately and a suitable therapy (e.g. vancomycin, 4 x 250 mg by oral route) has to be started. Drugs inhibiting peristalsis are contraindicated.

Cholestatic hepatitis
Cholestatic hepatitis is commonly reported with norfloxacin (*See section 4.8, Undesirable effects*). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Peripheral neuropathy
Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paraesthesias, hypoaesthesias, dysaesthesias and weakness have been reported in patients receiving quinolones, including norfloxacin. Norfloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of probenecid diminishes urinary excretion of norfloxacin without affecting its serum concentrations.

Antagonism has been demonstrated *in vitro* between norfloxacin and nitrofurantoin, as it is the case with other organic antibacterials. Therefore, norfloxacin should not be used together with nitrofurantoin.

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been rare reports of theophylline-related side effects in patients on concomitant therapy with norfloxacin and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted as required.

There are reports of elevated serum levels of ciclosporin with concomitant use of norfloxacin. If used concomitantly with norfloxacin ciclosporin serum levels should be monitored and its dosage appropriately adjusted.

Norfloxacin and other quinolones may enhance the effects of anticoagulants like warfarin or its derivatives. The interaction between quinolones and warfarin is mostly likely a result of inhibition of warfarin hepatic metabolism. When concomitant administration of these products is therapeutically necessary, prothrombin time should be monitored or other suitable coagulation tests be carried out.

Interaction with polyvalent cations in miscellaneous preparations (containing iron/antacids and products containing magnesium, aluminium, calcium or zinc):
Simultaneous administration of norfloxacin with multivitamin preparations containing calcium, preparations containing iron or zinc, antacids or sucralfate reduces the absorption of norfloxacin, leading to markedly decreased concentrations in serum and urine. Norfloxacin should therefore be taken either 2 hours before or at least 4 hours after such products. This restriction does not apply to H2-receptor antagonists.
Oral nutritional solutions and dairy products (milk or milk products such as yoghurt) reduce the absorption of norfloxacin. Norfloxacin should therefore be taken either 1 hour before or at least 2 hours after such products.

Some quinolones, including norfloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its half-life. This should be taken into consideration when consuming coffee as well as when using caffeine-containing drugs.

Concomitant administration of quinolones and fenbufen should be avoided, as animal data have shown that this combination can lead to convulsions.

4.6 Pregnancy and lactation

There is no evidence from animal studies that norfloxacin has any teratogenic or mutagenic effects. Embryotoxicity secondary to maternotoxicity was observed after large doses in rabbits. Embryonic losses were observed in cynomolgus monkeys without any teratogenic effects. The relevance of these findings for humans is uncertain.

The safe use of norfloxacin in pregnant women has not been established, but, as with other quinolones, norfloxacin has been shown to cause arthropathy in immature animals.
Pregnant women must not take norfloxacin.

There is no experience in humans on use during pregnancy and lactation.
Norfloxacin can be detected in amniotic fluid and umbilical cord blood. Quinolone-antibiotics are excreted in maternal milk.Therefore, norfloxacin must not be taken during lactation and breast-feeding must be discontinued during the treatment with norfloxacin.

4.7 Effects on ability to drive and use machines

Norfloxacin may alter patient’s reactivity so that ability to drive, operate machinery or work without firm support is impaired, especially at the start of treatment, on increasing the dose or when switching medication and in conjunction with alcohol.

4.8 Undesirable effects

System organ class	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1 000 to <1/100)**	**Rare (≥ 1/10 000 to <1/1000)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from the available data)**
Cardiac disorders				Prolonged QTc interval and ventricular arrhythmia (including torsades de pointes)	Tachycardia
Blood and lymphatic system disorders	Leucopenia, elevation of ALAT (SGPT), ASAT (SGOT), eosinophilia, neutropenia	Thrombocytopenia, Haemolytic anaemia, sometimes associated with glucose-6-phosphate dehydrogenase deficiency (*see section 4.4, Special warnings and precautions for use*)		Elevated levels of serum creatinine and blood urea nitrogen, elevated INR and thromboplastin time.	
Nervous system disorders	Headache, dizziness	Anorexia, sleep disturbances, polyneuropathy including Guillain-Barré syndrome, paraesthesia (*see section 4.4, Special warnings and precautions for use*)			
Eye disorders		Epiphora			
Ear and labyrinth disorders		Tinnitus			
Gastrointestinal disorders	Nausea, heartburn abdominal pain/cramps, diarrhoea	Flatulence, constipation, vomiting, pancreatitis	Pseudomembranous colitis (*see section 4.4, Special warnings and precautions for use*)		
Renal and urinary disorders		Interstitial nephritis	Renal failure		

System organ class	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1 000 to <1/100)**	**Rare (≥ 1/10 000 to <1/1000)**	**Very rare (<1/10,000)**	**Not known (cannot be estimated from the available data)**
Skin and subcutaneous tissue disorders	Rash	Photosensitivity: Stevens-Johnson syndrome; toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, pruritus, urticaria, angioedema (*see section 4.4, Special warnings and precautions for use*)			
Musculoskeletal and connective tissue disorders		Possible exacerbation of myasthenia gravis, arthritis, myalgia, arthralgia (*see section 4.4, Special warnings and precautions for use*)	Tendinitis or rupture of tendons, usually in combination with other risk factors like concomitant corticosteroids, advanced age or long-term dialysis. (*See section 4.3, Contraindications, and Contraindications*, and 4.4, *Special warnings and precautions for use*)	Rhabdomyolysis	
Vascular disorders		Vasculitis			
General disorders	Fever		Anaphylactic/ anaphylactoid reactions (see also sections 4.3, (*see section 4.4, Special warnings and precautions for use*)		
Immune system disorders					Hypersensitivity

System organ class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1 000 to <1/100)	Rare (≥ 1/10 000 to <1/1000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Psychiatric disorders		Depression, anxiety /nervousness, irritability, euphoria, disorientation, hallucination, confusion and psychic disturbances including psychotic reactions.			
Hepatobiliary disorders		Hepatitis including elevated liver function tests (*see section 4.4, Special warnings and precautions for use*)		Necrotising hepatitis	Jaundice (*see section 4.4, Special warnings and precautions for use*)
Reproductive system and breast disorders		Vaginal candidiasis			

4.9 Overdose

Gastrointestinal disturbances may occur in overdosage. In acute events induced vomiting or gastric lavage is necessary. Proper hydration should be maintained to prevent crystalluria.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic classification

Pharmaco-therapeutic group
Norfloxacin is a bactericidal antibiotic belonging to the group of fluoroquinolones.

ATC code
J01 MA 06

Mechanism of action

Mode of action
Norfloxacin inhibits bacterial deoxyribonucleic acid (DNA) synthesis by inhibition of bacterial topoisomerase II (gyrase) and topoisomerase IV..

Relationship between pharmacokinetics and pharmacodynamics
Efficacy is mainly dependent upon the Cmax (maximum serum concentration) : MIC (minimum inhibitory concentration) ratio of the pathogen and the AUC (area under the curve): MIK ratio of the pathogen, respectively.

Mechanism(s) of resistance
Resistance to norfloxacin can derive from the following mechanisms:

- Modified target structures: The main mechanism of resistance against norfloxacin and other fluoroquinolones consists in changes of topoisomerase II and IV as a result of mutation.
- Other mechanisms of resistance lead to reduced concentration of fluoroquinolones at the site of action. Therefor liable are a reduced penetration into the bacterial cell due to reduced formation of porins or an increased efflux out of the cell via efflux pumps.
- Transferable, plasmid-coded resistance was demonstrated in Escherichia coli and Klebsiella spp..

There is a partial or complete cross-resistance between norfloxacin and other fluoroquinolones.

Breakpoints
Testing of norfloxacin is performed by using the usual dilution series. The following minimum inhibitory concentrations were determined for sensitive and resistant micro-organisms:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) Breakpoints:

Species	**sensitive**	**resistant**
Enterobacteriaceae	≤ 0,5 mg/l	> 1 mg/l
Non-species related breakpoints*	≤ 0,5 mg/l	> 1 mg/l

* based mainly on serum pharmcokinetics

Prevalence of acquired resistance
The prevalence of resistance may vary geographically and with time for selected species.Data on the local resistance information are thus desirable, particularly in order to ensure adequate treatment of severe infections. If the local resistance situation puts the efficacy of norfloxacin in doubt, expert therapeutic advice should be sought. Particularly in cases of severe infection or unsuccessful therapy, a microbiological diagnosis with confirmation of the micro-organism and its sensitivity norfloxacin should be undertaken.

Prevalence of acquired resistance on the basis of data from the past 5 years from national resistance monitoring projects and studies (last revised: December 2007):

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Staphylococcus saprophyticus°
Aerobic Gram-negative micro-organisms
Enterobacter aerogenes
Enterobacter cloacae
Proteus vulgaris
Salmonella enterica (enteritis salmonella)°
Serratia marcescens
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Enterococcus faecalis§
Staphylococcus aureus (methicillin-sensitive)
Aerobic Gram-negative micro-organisms
Campylobacter jejuni$
Citrobacter freundii
Escherichia coli&
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus faecium
Staphylococcus aureus (methicillin-resistant)
Streptococcus agalactiae
Aerobic Gram-negative micro-organisms
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Clostridium difficile
Other micro-organisms
Chlamydia trachomatis
Mycoplasma hominis
Ureaplasma urealyticum

°*At the time of publication of the table, no current data were available. Sensitivity is assumed in the primary literature, standard works and therapy recommendations*

$*Most isolates show natural intermediate susceptibility.*

&*Resistance rate in isolates of patients with uncomplicated cystitis is < 10 %, in others > 10%*

5.2 Pharmacokinetic properties

Norfloxacin is rapidly absorbed from the gastrointestinal tract. Peak serum concentrations were observed 1 to 2 hours following oral administration.
Absorption from the gastrointestinal tract is about 30 - 40 % of the oral dose.
Steady state is achieved after 2 days.

Concentrations of 2.5 mg/l of norfloxacin in human serum lead to binding to plasma proteins of about 13.8%.Low protein binding enables rapid and extensive penetration into body tissues and fluids.

Distribution in body organs
Mean concentrations of norfloxacin in various fluids and tissues measured 1 - 4 hours after administration of two 400 mg oral doses show that the mean ratio of norfloxacin concentration ranged from 1.0 - 4.6 over serum concentration:

Body fluid or tissue	Concentration
Renal parenchyma	7.3 µg/g
Prostate	2.5 µg/g
Urinary bladder wall	3.0 µg/g
Seminal fluid	2.7 µg/ml
Testicle	1.6 µg/g
Uterus/cervix	3.0 µg/g
Vagina	4.3 µg/g
Bile	6.9 µg/ml

Urinary drug concentrations ranged between 100- to 300-fold greater than the concurrent serum concentrations.

Peak norfloxacin concentrations in the urine are about 100 times higher than the MIC_{90} for the majority of pathogens causing urinary tract infections.

Metabolism and elimination
Biotransformation of norfloxacin occurs in the liver. Six metabolites - all less active than norfloxacin - have been identified in urine; all modifications occurred on the terminal nitrogen of the piperazine ring. The major metabolite is an oxoderivative. None of the metabolites have been found in serum.

Norfloxacin is eliminated from the body through metabolism and by urinary and biliary excretion. Its biological half-life is 3 to 4 hours. Most of the dose is excreted in the urine after 24 hours, 26 - 32% as parent drug and 5 - 8% as metabolites. With the faeces about 30 - 40 % of the oral dose is excreted. After a single 400 mg dose of norfloxacin, mean antimicrobial activities equivalent to 278, 773 and 82 µg of norfloxacin/g of faeces were obtained at 12, 24 and 48 hours, respectively.
Renal excretion occurs by glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance of approx. 236 ± 56 ml/min. Total body-clearance amounts to 506 ± 211 ml/min.
After a single 400 mg dose, mean urinary concentrations of norfloxacin in healthy adults reached values of 417, 211, 100, 47 and 22 mg/l respectively (collected urine samples at 1-2, 3-4, 6-8, 8-12 and 12-24 hours after dosing).
In healthy elderly volunteers (65-75 years, normal kidney function corresponding to age) norfloxacin is excreted more slowly according to the physiologically reduced kidney function of this age-group. The absorption of the substance is apparently not influenced. The elimination half-life in geriatric patients was 2.7 to 3.5 hours (dose: 400 mg per day) and 5.3 to 5.4 h (dose: twice 400 mg per day) respectively.

Patients with impaired renal function
After a single dose of 400 mg, the availability of norfloxacin in patients with a creatinine-clearance of more than 30 ml/min x 1.73 m^2 is comparable to the availability in healthy volunteers. The renal excretion of norfloxacin is reduced at a creatinine-clearance below 30 ml/min x 1.73 m^2. The mean elimination half-life of norfloxacin in patients with creatinine-clearance of 30-80, 10-29 and less than 10 ml/min x 1.73 m^2 respectively was 4.4, 6.6 and 7.6 hours respectively. Peak serum concentrations of norfloxacin are apparently not influenced by renal insufficiency.

Effect of food on bioavailability
The presence of food does not significantly affect absorption, but prolongs the time to achieve peak plasma levels. However, milk and yoghurt have been shown to reduce absorption of quinolones, including norfloxacin.

5.3 Preclinical safety data

As with other quinolones, administration of norfloxacin led to arthropathies in immature animals. Following once daily administration of norfloxacin to young animals for seven days the minimum arthropathic norfloxacin dose in rats, rabbits and dogs was 100, 25 or 50 mg/kg body weight/die. At these dosages the serum peak concentration measured on day 6 was at 16.1, 9.7 or 5.1 mg/l. In weight-bearing joints, administration of norfloxacin led to lesions or erosion of the articular cartilage. In monkeys, arthropathies did not occur at norfloxacin dosages of less than 500 mg/kg body weight/die (C_{max} 15.6 mg/l). No similar pathology has been observed in adult animals. The peak serum levels measured in animal experiments at arthropatic dosages were far higher than the corresponding concentrations in children. However, due to the fact that clinical experience is limited, use of norfloxacin in children is not recommended.
Norfloxacin was tested in mice, rats, and rabbits up to the maternal toxic dose range. In cynomolgus monkeys and rabbits the number of viable foetuses was reduced at 200 mg/kg and 100 mg/kg. No dose or substance dependent malformations were observed.

Investigations on fertility and on perinatal and postnatal toxicity yielded no unfavourable effects.

Carcinogenicity:

Carcinogenicity studies in rats and mice did not yield indications of a carcinogenic potential of norfloxacin.

Genotoxicity and Tumorigenic Potential:

Norfloxacin can have genotoxic effects in mammalian cells by inhibition of topoisomerases. This effect has a threshold value which is not exceeded in therapeutic use.

There are no data on photomutagenicity/photocarcinogenicity of norfloxacin. Data on other fluoroquinolones suggest a weak photomutagenic or phototumorigenic effect of norfloxacin in vitro or in animal experiments.

Special toxicological properties:

To date there are no grounds for suspecting a potential cataractogenic effect following exposure to Norfloxacin. Corresponding experimental tests were not performed with norfloxacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Sodium starch glycollate, Type A
Microcrystalline cellulose
Colloidal anhydrous silica
Magnesium stearate
Purified water
Hypromellose
Talc
Titanium dioxide
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Blister strip comprising aluminium foil on one side and PVC/PVDC on the other.

Each carton folding box contains
6, 10, 14, 20 or 50 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

TAD Pharma GmbH,
Heinz-Lohmann-Strasse 5,
D-27472 Cuxhaven,
Germany.

8 MARKETING AUTHORISATION NUMBER

PA 0876/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 02 October 1998

Date of last renewal: 08 January 2008

10 DATE OF REVISION OF THE TEXT

November 2008