Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fenopine 100mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains100 mg of Ibuprofen.

Excipients with known effect
Liquid Maltitol (E965) 1ml/5ml
Sodium Methyl Parahydroxybenzoate (E219) 9.0mg/5ml
Sodium Propyl Parahydroxybenzoate (E217) 1.0mg/5ml
Propylene Glycol (E1520) 5.2 mg/5ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral suspension
White uniform suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fenopine 100 mg/5 ml Paediatric Oral Suspension is indicated for the symptomatic treatment of fever and of mild to moderate pain in children from 3 months weighing more than 5 kg to 12 years only.

4.2 Posology and method of administration

Posology
If in children aged from 6 months this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

For infants aged 3-5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persists.

Doses should be given approximately every 6 to 8 hours.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Paediatric population:
This product is not recommended for use in children below 3 months (5 kg), as there is insufficient experience of treatment in children of that age with ibuprofen.

The daily dosage is 20-30 mg/kg bodyweight in divided doses. Using the dosing device provided this can be achieved as follows:

Infants 3 – 6 months weighing more than 5 kg: One 2.5 ml (50 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Infants 6 – 12 months (weighing 8 – 10 kg): One 2.5 ml (50 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Infants and children 1 – 3 years (weighing 10 – 15 kg): One 5.0 ml (100 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Children 4 – 6 years (weighing 15 – 20 kg): One 7.5 ml (150 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Children 7 - 9 years (weighing 20 - 30 kg): One 10 ml (200 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Children 10 – 12 years (weighing 30 - 40 kg): One 15.0 ml (300 mg) dose Ibuprofen may be taken 3 times in 24 hours.

Adults and elderly:
This product is indicated for use in infants and children, and no dose instruction are given for adults and elderly.

Impaired renal function
In patients with mild or moderate reduction of renal function, the dose should be kept as low as possible for the shortest duration necessary to control symptoms and renal function monitored . (For patients with severe renal failure see section 4.3)

Impaired liver function
In patients with mild or moderate reduction of liver function the dose should be kept as low as possible for the shortest duration necessary to control symptoms and hepatic function monitored. (For patients with severe liver failure see section 4.3).

Method of administration
For oral administration and short term use only.
A double end spoon with measures of 2.5ml and 5ml is provided to ensure accuracy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with a history of bronchospasm asthma, rhinitis, or urticaria associated with the intake of aspirin (acetylsalicylic acid) or other non-steroidal anti-inflammatory drugs (NSAIDs).

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAID's therapy.

Severe hepatic failure, severe renal failure or severe heart failure (NYHA Class IV) or coronary heart disease (see section 4.4).

Last trimester of pregnancy (see section 4.6).

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Significant dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest possible duration necessary to control the symptoms (see section 4.2 and GI and cardiovascular risks below)

Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

Elderly:
The elderly have an increased frequency of adverse reaction to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

SLE and mixed connective tissue disease:
Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Asthmatic patients are to seek their doctor's advice before using ibuprofen (see below)

Other NSAIDs:
The use of Ibuprofen Oral Suspension with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5)

Gastrointestinal:
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8)
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oralcorticosteroids, or anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Renal:
Renal impairment as renal function may further deteriorate (see section 4.3 and 4.8)
Administration of NSAIDs such as Ibuprofen may cause dose dependent renal toxicity in patients with reduced renal blood flow or blood volume where renal prostaglandins support the maintenance of renal perfusion. Patients at risk of this reaction include those with impaired renal function, heart failure or liver dysfunction. This is of particular importance in hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur. Caution is therefore required in the use of Ibuprofen in such patients.
There is a risk of renal impairment in dehydrated children.

Hepatic:
Hepatic dysfunction (see section 4.3 and 4.8)

Respiratory:
Ibuprofen should be used with caution in patients with bronchial asthma or allergic disease, since such patients may have NSAID – sensitive asthma which has been associated with severe bronchospasm.

Cardiovascular and Cerebrovascular effects:
Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with history of hypertension and/or heart failure as fluid retention; hypertension and oedema have been reported in association with NSAIDs therapy.
Clinical studies suggest that use of ibuprofen, particularly at high doses (2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

Cases of Kounis syndrome have been reported in patients treated with Ibuprofen 100 mg/5 ml Paediatric Oral Suspension. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

Severe cutaneous adverse reactions (SCARs):
Severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see section 4.8). Most of these reactions occurred within the first month.

If signs and symptoms suggestive of these reactions appear ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of Ibuprofen Oral Suspension in case of varicella (Chicken pox.)

Masking of symptoms of underlying infections
Ibuprofen can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When ibuprofen is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In case of varicella, use of ibuprofen should be avoided due to the possible exacerbation of serious cutaneous and soft tissue infectious complications (see "severe skin reactions" above). In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Excipients:
Maltitol, Sodium methylhydroxybenzoate, sodium propylhydroxybenzoate, Propylene glycol and Sodium.
This medicine contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate may cause allergic reactions (possibly delayed).

This medicine contains 5.2 mg propylene glycol in each 5 ml which is equivalent to 0.832 mg/g. This should be considered in babies, in particular if given other medicines that contain propylene glycol or alcohol.

This medicine contains less than 1 mmol sodium (23 mg) per 5ml oral suspension, that is to say essentially "sodium-free".

The label will include:

Read the enclosed leaflet before taking this product.

Do not give this product if your baby or child

- Has (or has had two or more episodes of) a stomach ulcer, perforation or bleeding
- Is allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers

Speak to a pharmacist or your doctor before giving this product if your baby or child

- Has or has had asthma, diabetes, high cholesterol, high blood pressure, a stroke, liver, heart, kidney or bowel problems

Consult your doctor promptly if symptoms persist or worsen.

Do not exceed the stated dose.

Do not give to babies under 3 months of age.

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:
*Acetylsalicylic acid (*Aspirin): Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects (see section 4.4).
Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose

acetylsalicylic acid cannot be excluded . No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Other NSAIDs including cyclooxygenase-2 selective inhibitors: As a result of synergistic effects, avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Ticlopidine: NSAIDs should not be combined with ticlopidine due to a risk of an additive effect in the inhibition of the platelet function.

Methotrexate: There is a potential for an increase in plasma methotrexate.

Ibuprofen should be used with caution in combination with:
Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin or heparin (see section 4.4

Antihypertensives and diuretics: NSAIDs may diminish the effect of these drugs. Diuretic can increase risk of nephrotoxicity of NSAIDs.

Corticosteroids: increase the risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4)

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Ciclosporin: increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Lithium: There is evidence for potential increase in plasma levels of lithium.

Zidovudine: increase risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinoline may have increased risk of developing convulsions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.
In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

From the 20th week of pregnancy onward, ibuprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Ibuprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding
In limited studies, ibuprofen appears in the breast milk in very low concentration and is unlikely to affect the breast-fed infant adversely.

Fertility
The use of ibuprofen may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

4.7 Effects on ability to drive and use machines

As central nervous undesirable effects such as tiredness and dizziness may occur on use of ibuprofen at higher dosage, the ability to react and the ability to take part actively in road traffic and to operate machines may be impaired in isolated cases. This applies to a greater extent in combination with alcohol.

4.8 Undesirable effects

The following frequencies are taken as a basis when evaluating undesirable effects:
Very common: ³ 1/10
Common: ³ 1/100 to < 1/10
Uncommon: ³ 1/1,000 to < 1/100
Rare: ³ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known: cannot be estimated from the available data

Hypersensitivity reactions have been reported and these may consist of:

1. Non-specific allergic reactions and anaphylaxis
2. Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea.
3. Various skin reactions, e.g. pruritis, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Hypersensitivity reactions:

Uncommon: Hypersensitivity reactions with urticaria and pruritis.

Very rare: Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm.

Gastrointestinal Disorders:

The most commonly-observed adverse events are gastrointestinal in nature.

Uncommon: Abdominal pain, nausea and dyspepsia.

Rare: Diarrhoea, flatulence, constipation and vomiting.

Very rare: Peptic ulcer, perforation or gastrointestinal haemorrhage, melaena, haematemesis, sometimes fatal, particularly in the elderly. Ulcerative stomatitis, gastritis. Exacerbation of ulcerative colitis and Crohn's disease (see section 4.4)

Nervous System Disorders:

Uncommon: Headache

Very Rare: Aseptic meningitis – single cases have been reported very rarely.

Renal Disorders:

Very rare: Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Hepatic Disorders:

Very rare: Liver disorders.

HaematologicalDisorders:

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, panytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Skin and subcutaneous tissue disorders:

Uncommon: Various skin rashes

Very rare: Severe cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis).

Not-known: Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome). Acute generalised exanthematous pustulosis (AGEP). Photosensitivity reactions (frequency unknown). Fixed drug eruption.

Immune SystemDisorders:

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

Cardiovascular and CerebrovascularDisorders:

Not known: Kounis syndrome.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical studies suggest that use of ibuprofen (particularly at high doses 2400 mg/day) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear cut. The half-life in overdose is 1.5 – 3 hours.

Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within one hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non steroids; propionic acid derivatives

ATC code: M01AE01

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that in the conventional animal-experiment inflammation models, has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swelling and fever. Furthermore, ibuprofen reversibly inhibitsADP- and collagen-induced platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Absorption
On oral application ibuprofen is already partly absorbed in the stomach and then completely in the small intestine, peak serum concentrations occurring 1-2 hours after oral administration of a normal-release pharmaceutical form.

Distribution
Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%.

Biotransformation
Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination

Ibuprofen is metabolised in the liver into two major metabolites with primary excretion via the kidneys. Either as such or as major conjugates, together with negligible amount of unchanged Ibuprofen, Excretion by the kidney is both rapid and complete. Elimination half life is approximately 2 hours.

5.3 Preclinical safety data

As a well established and widely used product, the pre-clinical safety of ibuprofen is well documented.

The principal findings observed during subchronic and chronic toxicity studies with ibuprofen include gastric damage and ulcers. Any observation made during the in vitro and in vivo studies to investigate the mutagenic potential of ibuprofen were not considered to be clinically significant.

Furthermore no carcinogenic effects have been observed in mice and rats.
Ibuprofen inhibits ovulation in rabbits and impairs implantation in various animal species (rabbit, rat, and mouse). In reprotoxicity studies in rats and rabbits; ibuprofen crossed the placenta. At dose causing toxicity to the mother, malformations (ventricular septal defects) occurred more frequently in the progeny of rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Xanthan gum
Maltitol liquid (E965)
Polysorbate 80
Saccharin sodium (E954)
Citric acid monohydrate
Sodium methylhydroxybenzoate
Sodium propylhydroxybenzoate
Strawberry flavour *(*contains propylene glycol)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

An amber glass bottle sealed with child resistant, tamper evident cap.
An amber PET bottle sealed with child resistant, tamper evident cap. Pack sizes available: 50 ml, 100 ml, 150 ml and 200 ml. Not all pack sizes may be marketed.
A double ended spoon with measures of 2.5ml and 5ml is provided.

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

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/088/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd September 2010
Date of last renewal: 14th December 2023

10 DATE OF REVISION OF THE TEXT

December 2024