

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Visublend 0.3 mg/ml + 5 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

Excipient with known effect

Each ml of solution contains 0.05 mg of benzalkonium chloride.

Each ml of solution contains 0.95 mg phosphates.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to slightly yellow solution, practically free from foreign particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including older people)

The recommended dose is one drop of Visublend in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for Visublend suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing (see section 5.1).

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Renal and hepatic impairment

Visublend has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population

The safety and efficacy of Visublend in children aged 0 to 18 years has not been established. No data are available.

Method of administration

If more than one topical ophthalmic medicinal product is to be used, each one should be instilled at least 5 minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/bimatoprost) in Visublend may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

Visublend should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Endocrine disorders

Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic β -blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta- adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

β -blocking ophthalmological preparations may block systemic β -agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Hepatic

In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Ocular

Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased iris pigmentation, since these have been observed during treatment with bimatoprost and Visublend. Some of these changes may be permanent, and may lead to impaired field of vision and differences in appearance between the eyes when only one eye is treated (see section 4.8).

Macular oedema, including cystoid macular oedema, has been reported with Visublend. Therefore, Visublend should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

Visublend should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated

Skin

There is a potential for hair growth to occur in areas where Visublend solution comes repeatedly in contact with the skin surface. Thus, it is important to apply Visublend as instructed and avoid it running onto the cheek or other skin areas.

Excipients

The preservative in Visublend, benzalkonium chloride, may cause eye irritation. Contact lenses must be removed prior to application, with at least a 15-minute wait before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore monitoring is required with frequent or prolonged use of Visublend in dry eye patients or where the cornea is compromised.

Other conditions

Visublend has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

In studies of bimatoprost 0.3 mg/ml in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using Visublend with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with the bimatoprost / timolol fixed combination.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, Pregnancy and lactation

Pregnancy

There are no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women. Visublend should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost

No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol

Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Visublend is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Breast-feeding

Timolol

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to

produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost

It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. Visublend should not be used by breast-feeding women.

Fertility

There are no data on the effects of Visublend on human fertility.

4.7 Effects on ability to drive and use machines

Visublend has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Visublend

Summary of the safety profile

The adverse reactions reported in clinical studies using bimatoprost+timolol were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for Visublend have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using bimatoprost+timolol were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26% of patients and led to discontinuation in 1.5% of patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions that have been reported during clinical studies with all bimatoprost+timolol formulations (multi-dose and single-dose) (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency of possible adverse reactions listed below is defined using the following convention:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$

Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ to $< 1/1,000$
Very rare	$< 1/10,000$
Not known	Frequency cannot be estimated from available data

Table 1

System Organ Class	Frequency	Adverse reaction
<i>Immune system disorders</i>	Not known	hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
<i>Psychiatric disorders</i>	Not known	Insomnia ² , nightmare ²
<i>Nervous system disorders</i>	Common	headache
	Not known	Dysgeusia ² , dizziness
<i>Eye disorders</i>	Very common	conjunctival hyperaemia. Prostaglandin analogue periorbitopathy
	Common	punctuate keratitis, corneal erosion ² , burning sensation ² , conjunctival irritation ¹ , eye pruritus, stinging sensation in the eye ² , foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance ² , eyelid pruritus, visual acuity worsened ² , blepharitis ² , eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.
	Uncommon	iritis ² , conjunctival oedema ² ,
		eyelid pain ² , abnormal sensation in the eye ¹ , asthenopia, trichiasis ² , iris hyperpigmentation ² , eyelid retraction ² , eyelash discolouration (darkening) ¹ .
	Not known	cystoid macular oedema ² , eye swelling, vision blurred ² , ocular discomfort
<i>Cardiac disorders</i>	Not known	Bradycardia
<i>Vascular disorders</i>	Not known	Hypertension
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	Rhinitis ²
	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing

		bronchospastic disease) ² , asthma
<i>Skin and subcutaneous tissue disorders</i>	Common	blepharal pigmentation ² , hirsutism ² , skin hyperpigmentation (periocular).
	Not known	Alopecia, skin discolouration (periocular)
<i>General disorders and administration site conditions</i>	Not known	fatigue

¹adverse reactions only observed with bimatoprost+timolol single-dose formulation

²adverse reactions only observed with bimatoprost+timolol multi-dose formulation

Like other topically applied ophthalmic drugs, Visublend (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with Visublend are listed below in Table 2:

Table 2

System Organ Class	Adverse reaction
<i>Immune system disorders</i>	systemic allergic reactions including anaphylaxis ¹
<i>Metabolism and nutrition disorders</i>	hypoglycaemia ¹
<i>Psychiatric disorders</i>	depression ¹ , memory loss ¹ , hallucination ¹
<i>Nervous system disorders</i>	syncope ¹ , cerebrovascular accident ¹ , increase in signs and symptoms of myasthenia gravis ¹ , paraesthesia ¹ , cerebral ischaemia ¹
<i>Eye disorders</i>	decreased corneal sensitivity ¹ , diplopia ¹ , ptosis ¹ , choroidal detachment following filtration surgery (see section 4.4) ¹ , keratitis ¹ , blepharospasm ² , retinal haemorrhage ² , uveitis ² ,
<i>Cardiac disorder</i>	atrioventricular block ¹ , cardiac arrest ¹ , arrhythmia ¹ , cardiac failure ¹ , congestive heart failure ¹ , chest pain ¹ , palpitations ¹ , oedema ¹
<i>Vascular disorders</i>	hypotension ¹ , Raynaud's phenomenon ¹ , cold hands and feet ¹
<i>Respiratory, thoracic and mediastinal disorders</i>	Asthma exacerbation ² , COPD exacerbation ² , cough ¹
<i>Gastrointestinal disorders</i>	nausea ^{1,2} , diarrhoea ¹ , dyspepsia ¹ , dry mouth ¹ , abdominal pain ¹ , vomiting ¹
<i>Skin and subcutaneous tissue disorders</i>	psoriasisiform rash ¹ or exacerbation of psoriasis ¹ , skin rash ¹
<i>Musculoskeletal and connective tissue disorders</i>	myalgia ¹
<i>Reproductive system and breast disorders</i>	sexual dysfunction ¹ , decreased libido ¹
<i>General disorders and administration site conditions</i>	asthenia ^{1,2}
<i>Investigations</i>	liver function tests (LFT) abnormal ²

¹ adverse reactions observed with Timolol

² adverse reactions observed with Bimatoprost

Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including Visuplain can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with Visuplain and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of Visuplain may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevus or freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with Visuplain 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% and did not increase following 3 years treatment.

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

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 the

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

A topical overdose with Visublend is not likely to occur or to be associated with toxicity.

Bimatoprost

If Visublend is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m² is at least 70-times higher than the accidental dose of one bottle of Visublend in a 10 kg child.

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents – ATC code: S01ED51

Mechanism of action

Visublend consists of two active substances: bimatoprost and timolol. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. Bimatoprost +timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance . It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a β_1 and β_2 non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects

The IOP-lowering effect of bimatoprost+timolol is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for bimatoprost+timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population

The safety and efficacy of bimatoprost+timolol in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

Bimatoprost+timolol medicinal product

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost+timolol treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies where systemic absorption was measured, no accumulation was observed with either of the individual components.

Bimatoprost

Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean C_{max} and AUC_{0-24hrs} values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng.hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous

administration, was approximately 45 minutes; the total blood clearance was 1.5 l/hr/kg.

Characteristics in older people

After twice daily dosing, the mean AUC_{0-24hrs} value of 0.0634 ng.hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng.hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

Timolol

After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

5.3 Preclinical safety data

Bimatoprost+timolol medicinal product

Repeated dose ocular toxicity studies on bimatoprost+timolol showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of $\geq 0.03\%$ daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium hydrogen phosphate
Citric acid monohydrate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening of the bottle: to be used within 28 days. This medicinal product does not require any special storage conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

After first opening of the bottle:

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

White LDPE bottle with LDPE dropper and HDPE screw cap, with tamper evident ring. Each bottle has a fill volume of 3 ml.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

VISUfarma UK Ltd.
4230 Park Approach, Thorpe Park,
Leeds, LS15 8GB, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 52223/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2021

10 DATE OF REVISION OF THE TEXT

12/11/2024