

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nitoman 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of Tetrabenazine.

Excipients: Contains Lactose Monohydrate 64 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Yellowish-buff, circular, bevel-edged tablets having 'CL25' imprinted on one face and a single scoreline on the other.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the control of disorders of movement associated with organic disease of the central nervous system, such as Huntington's chorea, hemiballismus and senile chorea.

4.2 Posology and method of administration

Posology

Adults

Proper dosing of tetrabenazine involves careful titration of therapy to determine an individualised dose for each patient. When first prescribed, tetrabenazine therapy should be titrated slowly over several weeks to allow the identification of a dose for chronic use that reduces chorea and is well tolerated.

Dosage and administration are variable and only a guide is given. Starting doses should be 12.5 mg to 25 mg per day and should be titrated up slowly every 4 to 7 days to allow identification of a dose that is efficacious and well tolerated. After titration is initiated, the total daily dose should be given in two to three divided doses. Titration can be up to 200 mg per day or dose-limiting adverse events, whichever happens first. If the adverse event does not resolve, after dose reduction, consideration should be given to withdrawing tetrabenazine treatment.

If there is no improvement at the maximum dose in seven days, it is unlikely that the compound will be of benefit to the patient, either by increasing the dose or by extending the duration of treatment.

Discontinuation of Treatment with Tetrabenazine

Discontinuation of tetrabenazine is associated with the return of chorea (without significant worsening compared to baseline). Other adverse reactions to sudden treatment withdrawal are possible but unlikely and generally mild.

Resumption of Treatment

Following treatment interruption of greater than 5 days or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications, tetrabenazine therapy should be retitrated when resumed. The dose should be initiated at 12.5 mg twice a day, wait 7 days then titrate up by 12.5 mg per day. For short-term treatment interruption of less than 5 days, treatment can be resumed at the previous maintenance dose without titration.

If adverse events such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety, or intolerable sedation occur, titration should be stopped and the dose should be reduced.

Elderly

No specific studies have been performed in the elderly.

Paediatric population

The safety and efficacy of tetrabenazine in children have not been established.

Other information

Hepatic Insufficiency

A study in hepatically impaired subjects has shown that there is a markedly decreased metabolism of tetrabenazine to its metabolites with a higher mean C_{max} in hepatically impaired subjects in comparison with healthy subjects. The elimination half life of tetrabenazine and its metabolites in subjects with hepatic impairment was also prolonged.

Increased exposure to other circulating metabolites and the contribution of tetrabenazine or those metabolites to safety and efficacy are unknown. Therefore, tetrabenazine is contraindicated in patients with hepatic impairment, Child Pugh 5 to 9 (see section 5.2).

Renal Insufficiency

The use of tetrabenazine in patients with renal insufficiency has not been studied.

Method of administration

The tablets are for oral administration.

4.3 Contraindications

Tetrabenazine is contraindicated in patients:

- - With hypersensitivity to the active substance (tetrabenazine) or to any of the excipients listed in section 6.1
- - Who are actively suicidal
- - With untreated or inadequately treated depression
- - Who are breast-feeding
- - Taking or who have taken within 14 days a monoamine oxidase inhibitor (MAOI) (see section 4.4, 4.5 and 4.8)
- - With impaired hepatic function, Child-Pugh 5 to 9
- - Taking reserpine (see section 4.5)
- - With parkinsonism and hypokinetic-rigid syndrome

4.4 Special warnings and precautions for use

The dose of tetrabenazine should be titrated to determine the most appropriate dose for each patient. In vitro and in vivo studies indicate that the tetrabenazine metabolites α - HTBZ and β - HTBZ are substrates for CYP2D6 (see section 5.2).

Therefore dosing requirements may be influenced by a patient's CYP2D6 metaboliser status and concomitant medications which are strong CYP2D6 inhibitors (see section 4.5).

When first prescribed, tetrabenazine therapy should be titrated slowly over several weeks to allow the identification of a dose that both reduces chorea and is well tolerated. If the adverse effect does not resolve or decrease, consideration should be given to discontinuing tetrabenazine.

Once a stable dose has been achieved, treatment should be reassessed periodically in the context of the patient's underlying condition and their concomitant medications (see section 4.5).

Depression / Suicidality

Tetrabenazine may cause depression or worsen pre- existing depression. Cases of suicidal ideation and behavior have been reported in patients taking this product. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation (see also section 4.3).

Patients should be closely monitored for the emergence of such adverse events and patients and their caregivers should be informed of the risks and instructed to report any concerns to their doctor immediately.

If depression or suicidal ideation occurs, it may be controlled by reducing the dose of tetrabenazine and/or initiating antidepressant therapy. If depression or suicidal ideation is profound, or persists, discontinuation of tetrabenazine and initiation of antidepressant therapy should be considered.

Anger and Aggression

There is a potential risk of anger and aggressive behavior occurring or worsening in patients taking tetrabenazine with a history of depression or other psychiatric illnesses.

Parkinsonism

Tetrabenazine can induce parkinsonism and exacerbate pre-existing symptoms of Parkinson's disease. The tetrabenazine dose should be adjusted as clinically indicated to minimise this side effect.

Dysphagia

Dysphagia is a component of Huntington's disease. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia may be associated with aspiration pneumonia. In clinical trials, some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

Tardive Dyskinesia

Pre-synaptic dopamine depletion could theoretically lead to supersensitivity to dopamine. Tetrabenazine is a central monoamine depleting agent which can cause extrapyramidal symptoms and theoretically cause tardive dyskinesia in humans.

There have been cases of tardive dyskinesia with tetrabenazine reported in the literature and in post-marketing; therefore, physicians should be aware of the possible risk. If signs and symptoms of tardive dyskinesia appear in a patient treated with tetrabenazine, drug discontinuation should be considered.

Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in patients treated with tetrabenazine and other drugs that reduce dopaminergic transmission. This may occur soon after initiation of therapy, following changes in dosage or after prolonged treatment. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. If NMS is suspected, tetrabenazine should be withdrawn immediately and appropriate supportive therapy instituted.

If the patient requires treatment with tetrabenazine after recovery from NMS, the potential reintroduction of therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

QTc Prolongation

Tetrabenazine causes a small increase (about 8 msec) in the corrected QT interval. Tetrabenazine should be used with caution with other drugs known to prolong QTc and in patients with congenital long QT syndromes and a history of cardiac arrhythmias (see section 4.5).

Cardiac Disease

Tetrabenazine has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

Akathisia, Restlessness, and Agitation

Patients taking tetrabenazine should be monitored for the presence of akathisia and also for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia, the tetrabenazine dose should be reduced. Some patients may require discontinuation of therapy.

Sedation and Somnolence

Sedation is the most common dose-limiting adverse effect of tetrabenazine. Patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of tetrabenazine and know how the drug affects them.

Orthostatic Hypotension

Tetrabenazine may induce postural hypotension at therapeutic doses, and symptoms may include postural dizziness and syncope. This should be considered in patients who may be vulnerable to hypotension or its effects. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

Hyperprolactinemia

Tetrabenazine elevates serum prolactin concentrations in humans. Following administration of 25 mg to healthy volunteers, peak plasma prolactin levels increased 4- to 5 - fold. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin- dependent *in vitro*, a factor of potential importance if tetrabenazine is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecomastia and impotence can be caused by elevated serum concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown.

Chronic increase in serum prolactin levels (although not evaluated in the tetrabenazine development program) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of tetrabenazine.

Binding to Melanin- Containing Tissues

Since tetrabenazine or its metabolites bind to melanin - containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use. The clinical relevance of tetrabenazine's binding to melanin - containing tissues is unknown.

Although there are no specific recommendations for periodic ophthalmic monitoring, prescribers should be aware of the possibility of ophthalmologic effects after long term exposure.

Drug- Disease Interactions

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose - galactose malsorption should not take this medicine.

Laboratory Tests

No clinically significant changes in laboratory parameters were reported in clinical trials with tetrabenazine. In controlled clinical trials, tetrabenazine caused a small mean increase in ALT and AST laboratory values as compared to placebo.

Elderly

The pharmacokinetics of tetrabenazine and its primary metabolites have not been formally studied in geriatric subjects.

Paediatric Population

The safety and efficacy of tetrabenazine in children have not been established.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed *in vivo*. The metabolising enzymes of tetrabenazine are partly unknown.

In vitro-studies indicate that tetrabenazine may be an inhibitor of CYP2D6 and therefore may cause increased plasma concentrations of medicinal products metabolised via CYP2D6, e.g. metoprolol, amitriptyline, imipramine, haloperidol, and risperidone.

Patients Taking CYP2D6 Inhibitors

In vitro and *in vivo* studies indicate that the tetrabenazine metabolites α -HTBZ and β -HTBZ are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine given after 10 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily. There was approximately 30% increase in C_{max} and an approximately 3-fold increase in AUC for α -HTBZ in subjects given paroxetine prior to tetrabenazine compared to tetrabenazine given alone. For β -HTBZ, C_{max} and AUC were increased 2.4- and 9-fold, respectively, in subjects given paroxetine prior to tetrabenazine given alone. The elimination half-life of α -HTBZ and β -HTBZ was approximately 14 hours when tetrabenazine was given with paroxetine. Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, or quinidine) to a patient already receiving a stable dose of

tetrabenazine and a reduction in the dose of tetrabenazine should be considered. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated.

Other Cytochrome P450 inhibitors: Based on *in vitro* studies, a clinically significant interaction between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) is not likely.

Levodopa

Tetrabenazine inhibits the action of levodopa and thereby attenuates its effect.

Monoamine Oxidase Inhibitors

Tetrabenazine should not be administered in the presence of MAOIs because of the risk of possible serious interactions resulting in hypertensive crisis (see section 4.3). At least 14 days should elapse between the discontinuation of MAOI and initiation of treatment with tetrabenazine.

Concomitant Use of Neuroleptic Drugs

Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists. There is a potential for significant dopamine depletion when administering tetrabenazine concomitantly with neuroleptic agents (e.g. haloperidol, chlorpromazine, metoclopramide, etc.) and patients should be monitored clinically for the development of parkinsonism.

Antihypertensive Drugs and Beta-Blockers

The concurrent use of tetrabenazine with antihypertensive drugs and beta-blockers may increase the risk of orthostatic hypotension.

Interaction with CNS Depressants

The possibility of additive sedative effects should be considered when tetrabenazine is used in conjunction with CNS depressants (including alcohol, neuroleptics, hypnotics, and opioids).

Medicines known to Prolong QTc

Tetrabenazine should be used with caution with drugs known to prolong QTc including antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin) and Class IA and III antiarrhythmic medications (e.g., quinidine, procainamide, amiodarone, sotalol).

Reserpine

Concomitant use of tetrabenazine and reserpine is contraindicated (see section 4.3). Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Caution should therefore be used when switching a patient from reserpine to tetrabenazine. The physician should wait for chorea to re-emerge before administering tetrabenazine to avoid overdosage and major depletion of serotonin and norepinephrine in the CNS. Since the effects of reserpine can be prolonged, clinical judgment and caution should be used regarding time to discontinuation before starting tetrabenazine.

Digoxin

Digoxin is a substrate for P-glycoprotein. A study in healthy volunteers showed that tetrabenazine (25 mg twice daily for 3 days) did not affect the bioavailability of digoxin, suggesting that at this dose, tetrabenazine does not affect P-glycoprotein in the intestinal tract. *In vitro* studies also do not suggest that tetrabenazine or its metabolites are P-glycoprotein inhibitors.

Paediatric Population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well controlled studies for the use of tetrabenazine in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Tetrabenazine is not recommended during pregnancy and in women of childbearing potential not using contraception.

The effect of tetrabenazine on labour and delivery in humans is unknown.

Lactation

It is unknown whether tetrabenazine or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Tetrabenazine is contra-indicated during breast-feeding (see section 4.3).

Fertility

In animal studies with tetrabenazine there was no evidence of effect on pregnancy or *in utero* survival. Female cycle lengths were increased and a delay in fertility was seen.

4.7 Effects on ability to drive and use machines

Tetrabenazine may cause drowsiness and therefore may impair the ability to drive and use machines.

4.8 Undesirable effects

System/organ categories			Reactions			
	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to ≤1/100)	Rare (≥ 1/10,000 to ≤1/1,000)	Very rare (≤1/10,000)	Not known (cannot be estimated from the available data)
Blood & lymphatic system disorders					Leukopaenia, Neutropenia	
Immune system disorders					Hypersensitivity	
Metabolism and nutrition disorders		Decreased appetite			Dehydration	Increased appetite
Psychiatric disorders	Depression, Anxiety, Restlessness, Confusion	Irritability, Obsessive-compulsive disorder, Agitation			Aggression, Anger, Suicidal ideation, Suicide attempt, Nervousness, Sleep disorder	
Nervous system disorders	Sedation/ Somnolence/ Drowsiness, Extrapyrarnidal event, Insomnia, Akathisia	Parkinsonism (may include balancing problems), Gait imbalance/balance difficulty, Bradykinesia, Dystonia, Lethargy, Dizziness, Dysarthria, Headache			Neuroleptic malignant syndrome, Ataxia, Tremor, Excess salivation	Memory loss
Eye disorders	Blepharospasm				Oculogyric crisis, Photophobia	
Cardiac disorders					Palpitations	
Vascular disorders					Hypertension	Postural hypotension, Hypertens

						ive crisis
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection	Pneumonia, Dyspnoea, Bronchitis			Cough, Pneumonia aspiration	
Gastro-intestinal disorders	Nausea	Diarrhoea, Vomiting, Constipation		Dysphagia	Dry mouth	
Heptaobiliary disorders						Increased ALT, Increased AST
Skin & subcutaneous tissue disorders					Hyperhidrosis, Rash, Pruritus, Urticaria	
Renal and urinary disorders		Dysuria			Urinary tract infection	
Reproductive system and breast disorders					Irregular menstrual cycle/ amenorrhea/ menstrual disorders	
General disorders and administration site conditions	Fatigue	Ecchymosis			Malaise, Pyrexia, Drug interaction	Weakness
Investigations					Weight decreased	Weight increased
Injury, poisoning and procedural complications	Fall	Laceration, Inflicted injury		Drug administration error	Overdose	

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, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms associated with overdoses of tetrabenazine may include acute dystonia, oculogyric crisis, nausea, vomiting, diarrhoea, sweating, hypotension, confusion, hallucinations, hypothermia, sedation, rubor and tremor.

Treatment should consist of those general measures employed in the management of overdosage with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control centre on the treatment of any overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC Code: NO7XX06.

Tetrabenazine is a synthetic derivative of benzylquinolizine that causes depletion of dopamine and other monoamines in the central nervous system.

The precise mechanism by which tetrabenazine exerts its effects is unknown, but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

Studies conducted *in vitro* and *in vivo* have shown that tetrabenazine is a selective inhibitor of monoamine transportation into pre-synaptic neuronal vesicles, by reversible inhibition of the VMAT2 (vesicular monoamine transporter 2), which is principally located in the central nervous system. Studies have shown that α -dihydrotetrabenazine, one of the principal metabolite of tetrabenazine, has a similar affinity and more significant selectivity for VMAT2.

At a synaptic level tetrabenazine and α -dihydrotetrabenazine creates a reversible depletion of monoamines in the presynaptic terminals. Within the CNS tetrabenazine and α -dihydrotetrabenazine causes preferential depletion of dopamine from nerve terminals. Neurotransmitter depletion by a single dose of tetrabenazine is reversible and lasts only a few hours.

5.2 Pharmacokinetic properties

Absorption and Distribution

Tetrabenazine is quickly and mostly absorbed after oral administration. Its absorption is not affected by the taking of food.

Clinical testing has shown that a single oral dose of tetrabenazine undergoes extensive (>75%) absorption from the gastro-intestinal tract.

After single oral doses ranging from 12.5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection because of the rapid and extensive hepatic metabolism of tetrabenazine to α -HTBZ and β -HTBZ. α -HTBZ and β -HTBZ are metabolized principally by CYP2D6. Peak plasma concentrations (C_{max}) of α -HTBZ and β -HTBZ are reached within 1 to 1½ hours post-dosing. α -HTBZ and β -HTBZ are subsequently metabolized to another major circulating metabolite, O-dealkylated-HTBZ, for which C_{max} is reached approximately 2 hours post-dosing.

The *in vitro* protein binding of tetrabenazine, α -HTBZ, and β -HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine binding ranged from 82% to 85%, α -HTBZ binding ranged from 60% to 68%, and β -HTBZ binding ranged from 59% to 63%.

Biotransformation

The metabolism of tetrabenazine is complex, initially proceeding via the formation of alpha and beta dihydrotetrabenazine. α -HTBZ and β -HTBZ, major circulating metabolites, have half-lives of 4-8 hours and 2-4 hours, respectively. The majority of the observed metabolites appear to be formed from these dihydrotetrabenazines as a result of O-dealkylation, hydroxylation and conjugation.

Elimination

After oral administration, tetrabenazine is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. Clinical testing has shown that subjects with liver impairment have substantially reduced first-pass systemic metabolism of tetrabenazine, resulting in increased exposure to the parent compound compared to healthy subjects. The conversion of tetrabenazine to alpha and beta dihydrotetrabenazine appears to be slower in subjects with liver impairment as is the subsequent elimination of these metabolites.

No significant build-up has been observed after daily administration. The elimination half-life of dihydrotetrabenazine is approximately five hours.

Tetrabenazine is mostly eliminated in metabolised form in urine (less than 2% of tetrabenazine is excreted in unchanged form).

Linearity

After administration of single doses from 12.5 to 50 mg of tetrabenazine, the maximum plasma concentration and the area under the curve increased in proportion to the dose, indicating a linear kinetic.

5.3 Preclinical safety data

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

In repeated dose toxicity studies orally administered tetrabenazine is generally well tolerated across all animal species tested. Most effects observed are related to the pharmacological parameters of the drug and reflect central monoamine depletion.

These signs typically include hypoactivity, lethargy, squinted eyes, or eyes closed. They last up to several hours after dosing and in some species at high doses interfere with normal food intake with consequent decreased or suppressed body weight gain. Across all animal species tested dose-dependent sedation is the dose limiting effect and the principal adverse effect following oral administration of tetrabenazine.

Tetrabenazine and metabolites α -HTBZ and β -HTBZ were negative in the in vitro bacterial reverse mutation assay. Tetrabenazine was clastogenic in the in vitro chromosome aberration assay in Chinese hamster ovary cells in the presence of metabolic activation. α -HTBZ and β -HTBZ were clastogenic in the in vitro chromosome aberration assay in Chinese hamster lung cells in the presence and absence of metabolic activation. Tetrabenazine was negative in male mice and rats but equivocal in female rats in in vivo micronucleus tests.

Tetrabenazine did not cause an increase in any tumor type when administered for 26 weeks in the transgenic p53 heterozygous mouse model at doses up to 30 mg/kg/day. Tetrabenazine was non-carcinogenic when administered for 94 weeks to male rats at doses up to 12 mg/kg/day.

Tetrabenazine was not teratogenic to rats or rabbits at the maximum recommended human dose (MRHD) (3 or 13-fold, respectively). In prenatal/postnatal toxicity studies, tetrabenazine increased stillborn pups and neonatal mortality as well as delayed pup maturation in rats. These effects could either be indirect effects due to inadequate maternal care or a direct effect of tetrabenazine on the pups. The no-effect dose was 0.5 times the MRHD.

In a fertility and early embryonic development study at systemic exposures below clinical levels there was no effect on pregnancy or in utero survival in rats but estrous cycle length was increased and a delay in fertility was seen in female rats. Reproduction was unaffected in male rats.

Tetrabenazine and metabolites accumulate in melanin-containing tissues in partially pigmented rats. A single oral administration of ^{14}C -tetrabenazine to Lister Hooded rats resulted in high levels of radioactivity that persisted in pigmented tissues (eye, uveal tract and pigmented fur) and were still measurable 21 days after administration while all other tissues were BLQ (Below Limit of Quantification).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Talc
Magnesium Stearate
Iron Oxide Yellow, (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Five years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

A white HDPE bottle containing 112 tablets with a white HDPE cap.

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

Bausch Health Ireland Limited
3013 Lake Drive
Citywest Business Campus
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Ireland

8 MARKETING AUTHORISATION NUMBER

PA22698/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1994

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

May 2019