Summary Product Characteristics

1. Name of the proprietary product: NCI Brimonidine Eye Drops

Name of the non-proprietary International Product: Brimonidine Ophthalmic Solution

Route of Administration: Ocular

2. Qualitative and Quantitative composition:

SR. No.	Ingredients	Specification	Label Claim	Qty/ml (mg)	% OA	Qty/ml With OA (mg)	Reason for inclusion
1.	Brimonidine Tartrate	IH	0.1% w/v	1.00	10 %	1.10	Active
2.	Stabilized Oxychloro complex	IH	0.005 % v/v	0.06	--	0.06	Preservative
3.	Polyvinyl alcohol	BP	--	5.00	--	5.00	Lubricant
4.	Citric acid	BP	--	5.00	--	5.00	Buffering Agent
5.	Sodium chloride	BP	--	3.50	--	3.50	Buffering Agent
6.	Tri Sodium Citrate	BP	--	19.00	--	19.00	Buffering Agent
7.	Water for Injection	BP	--	q.s. to 1ml	--	q.s. to 1 ml	Vehicle

BP = British Pharmacopoeia

IH = In-House Specification

q.s. = Quantity Sufficient

* Quantity of active ingredients to be taken by consideration of their assay and water content.

3. Pharmaceutical Form: Ophthalmic solution

4. Clinical Particulars:

4.1 Therapeutic Indications

4.1 Therapeutic Indications:

Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

− As monotherapy in patients in whom topical beta-blocker therapy is contraindicated.

− As adjunctive therapy to other intraocular pressure lowering medications when the target IOP is not achieved with a single agent.

4.2 Posology and method of administration:

The recommended dose is one drop of Brimonidine Ophthalmic Solution in the affected eye(s) three times daily, approximately 8 hours apart.

Brimonidine Ophthalmic Solution ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is being used, the products should be administered at least 5 minutes apart.

4.3 Contraindications

− Hypersensitivity to the active substance or to any of the excipients.

− Neonates and infants.

− Patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

4.4 Special warnings and precautions for use

Children of 2 years of age and above, especially those in the 2-7 age range and/or weighing ≤ 20 Kg, should be treated with caution and closely monitored due to the high incidence and severity of somnolence.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease.

Some (12.7%) patients in clinical trials experienced an ocular allergic type reaction with Brimonidine Ophthalmic Solution. If allergic reactions are observed, treatment with Brimonidine Ophthalmic Solution should be discontinued.

Delayed ocular hypersensitivity reactions have been reported with Brimonidine Ophthalmic Solution 0.2%, with some reported to be associated with an increase in IOP.

Brimonidine Ophthalmic Solution should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangiitis obliterans.

Brimonidine Ophthalmic Solution has not been studied in patients with hepatic or renal impairment; caution should be used in treating such patients.

The preservative in Brimonidine Ophthalmic Solution, benzalkonium chloride, may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

Brimonidine Ophthalmic Solution is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenagic transmission (e.g. tricyclic antidepressants and miaserin.

Although specific drug interactions studies have not been conducted with Brimonidine Ophthalmic Solution, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

No data on the level of circulating catecholamines after Brimonidine Ophthalmic Solution administration are available. Caution, however, is advised in patients taking medications which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

After the application of BrimonidineOphthalmic Solution, clinically insignificant decreases in blood pressure were noted in some patients. Caution is advised when using drugs such as antihypertensives and/or cardiac glycosides concomitantly with Brimonidine Ophthalmic Solution.

Caution is advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity i.e. agonists or antagonists of the adrenergic receptor e.g. (isoprenaline, prazosin).

4.6 Pregnancy and Lactation:

The safety of use during human pregnancy has not been established. In animal studies, brimonidine did not cause any teratogenic effects. In rabbits, brimonidine, at plasma levels higher than are achieved during therapy in humans, has been shown to cause increased preimplantation loss and postnatal growth reduction. Brimonidine Ophthalmic Solution should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

It is not known if brimonidine is excreted in human milk. The compound is excreted in the milk of the lactating rat. Brimonidine Ophthalmic Solution should not be used by women nursing infants.

4.7 Effects on the ability to drive and use machines

Brimonidine Ophthalmic Solution may cause fatigue and/or drowsiness, which may impair the ability to drive or operate machinery. Brimonidine Ophthalmic Solution may cause blurred and/or abnormal vision, which may impair the ability to drive or to use machinery, especially at night or in reduced lighting. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8 Undesirable effects:

The most commonly reported ADRs are oral dryness, ocular hyperaemia and burning/stinging, all occurring in 22 to 25% of patients. They are usually transient and not commonly of a severity requiring discontinuation of treatment.

Symptoms of ocular allergic reactions occurred in 12.7% of subjects (causing withdrawal in 11.5% of subjects) in clinical trials with the onset between 3 and 9 months in the majority of patients.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of undesirable effects: 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).

Cardiac disorders

Uncommon: palpitations/arrhythmias (including bradycardia and tachycardia)

Nervous system disorders

Very common: headache, drowsiness

Common: dizziness, abnormal taste

Very rare: syncope

Eye disorders

Very common:

− ocular irritation (hyperaemia, burning and stinging, pruritus, foreign body sensation, conjunctival follicles)

− blurred vision

− allergic blepharitis, allergic blepharoconjunctivitis, allergic conjunctivitis, ocular allergic reaction, and follicular conjunctivitis

Common:

− local irritation (eyelid hyperaemia and oedema, blepharitis, conjunctival oedema and discharge, ocular pain and tearing)

− photophobia

− corneal erosion and staining

− ocular dryness

− conjunctival blanching

− abnormal vision

− conjunctivitis

Very rare:

− iritis

− miosis

Respiratory, thoracic and mediastinal disorders

Common: upper respiratory symptoms

Uncommon: nasal dryness

Rare: dyspnoea

Gastrointestinal disorders

Very common: oral dryness

Common: gastrointestinal symptoms

Vascular disorders

Very rare: hypertension, hypotension

General disorders and administration site conditions

Very common: fatigue

Common: asthenia

Immune system disorders

Uncommon: systemic allergic reactions

Psychiatric disorders

Uncommon: depression

Very rare: insomnia

The following adverse reactions have been identified during post-marketing use of Brimonidine Ophthalmic Solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made:

Not known:

Eye disorders

- iridocyclitis (anterior uveitis)

- eyelid pruritus

Skin and subcutaneous tissue disorders

- Skin reaction including erythema, face oedema, pruritus, rash and vasodilatation

In cases where brimonidine has been used as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported in neonates and infants receiving brimonidine.

In a 3-month, phase 3 study in children aged 2-7 years with glaucoma, inadequately controlled by beta-blockers, a high prevalence of somnolence (55%) was reported with Brimonidine Ophthalmic Solution as adjunctive treatment. In 8% of children, this was severe and led to discontinuation of treatment in 13%. The incidence of somnolence decreased with increasing age, being least in the 7-year-old age group (25%), but was more affected by weight, occurring more frequently in those children weighing ≤20 kg (63%) compared to those weighing >20 kg (25%).

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose:

Ophthalmic overdose (Adults):

In those cases received, the events reported have generally been those already listed as adverse reactions.

Systemic overdose resulting from accidental ingestion (Adults):

There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension. It was reported that the hypotensive episode was followed by rebound hypertension.

Treatment of oral overdose includes supportive and symptomatic therapy; patient's airways should be maintained.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population

Reports of serious adverse effects following inadvertent ingestion of Brimonidine Ophthalmic Solution by paediatric subjects have been published or reported to Allergan. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6-24 hours.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sympathomimetics in glaucoma therapy

ATC Code: S01EA 05

Brimonidine is an alpha-2 adrenergic receptor agonist that is 1000-fold more selective for the alpha-2 adrenoceptor than the alpha-1 adrenoreceptor.

This selectivity results in no mydriasis and the absence of vasoconstriction in microvessels associated with human retinal xenografts.

Topical administration of brimonidine tartrate decreases intraocular pressure (IOP) in humans with minimal effect on cardiovascular or pulmonary parameters.

Limited data are available for patients with bronchial asthma showing no adverse effects.

Brimonidine Ophthalmic Solution has a rapid onset of action, with peak ocular hypotensive effect seen at two hours post-dosing. In two 1 year studies, Brimonidine Ophthalmic Solution lowered IOP by mean values of approximately 4-6 mmHg.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action. It is thought that Brimonidine Ophthalmic Solution may lower IOP by reducing aqueous humour formation and enhancing uveoscleral outflow.

Clinical trials show that Brimonidine Ophthalmic Solution is effective in combination with topical beta-blockers. Shorter term studies also suggest that Brimonidine Ophthalmic Solution has a clinically relevant additive effect in combination with travoprost (6 weeks) and latanoprost (3 months).

5.2 Pharmacokinetic properties

a) <u>General characteristics</u>

After ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations were low (mean Cmax was 0.06 ng/ml). There was a slight accumulation in the blood after multiple (2

times daily for 10 days) instillations. The area under the plasma concentration-time curve over 12 hours at steady state (AUC_0-12h) was 0.31 ng·hr/ml, as compared to 0.23 ng·hr/ml after the first dose. The mean apparent half-life in the systemic circulation was approximately 3 hours in humans after topical dosing.

The plasma protein binding of brimonidine after topical dosing in humans is approximately 29%.

Brimonidine binds reversibly to melanin in ocular tissues, in vitro and in vivo. Following 2 weeks of ocular instillation, the concentrations of brimonidine in iris, ciliary body and choroid-retina were 3- to 17-fold higher than those after a single dose. Accumulation does not occur in the absence of melanin.

The significance of melanin binding in humans is unclear. However, no significant ocular adverse reaction was found during biomicroscopic examination of eyes in patients treated with Brimonidine Ophthalmic Solution for up to one year, nor was significant ocular toxicity found during a one year ocular safety study in monkeys given approximately four times the recommended dose of brimonidine tartrate.

Following oral administration to man, brimonidine is well absorbed and rapidly eliminated. The major part of the dose (around 75% of the dose) was excreted as metabolites in urine within five days; no unchanged drug was detected in urine. In vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Kinetics profile:

No great deviation from dose proportionality for plasma Cmax and AUC was observed following a single topical dose of 0.08%, 0.2% and 0.5%.

b) Characteristics in patients

Characteristics in elderly patients:

The C_{max}, AUC, and apparent half-life of brimonidine are similar in the elderly (subjects 65 years or older) after a single dose compared with young adults, indicating that its systemic absorption and elimination are not affected by age.

Based on data from a 3 month clinical study, which included elderly patients, systemic exposure to brimonidine was very low.

5.3 Pre-clinical Safety:

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:

List of Excipients:

Stabilized Oxychloro complex	IH
Polyvinyl alcohol	BP
Citric acid	BP
Sodium chloride	BP
Tri Sodium Citrate	BP
Water for Injection	BP

6.2 Incompatibilities: None are known

6.3 Shelf Life: 24 months. Discard 28 days after first opening.

6.4 Special Precautions for storage:

Store in a cool and dry place.

6.5 Nature and contents of container:

10 ml sterile plastic vial to be packed in primary carton along with the pack insert.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing Authorization Holder:

NCI Pharm Chem Ind. Ltd.
29 Igbehinadun Street,
Oshodi. Lagos, Nigeria.

8. Marketing Authorization Number: ---

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: June 2017