AUSTRALIAN PRODUCT INFORMATION – ILEVRO® (NEPAFENAC) EYE DROPS SUSPENSION

1 NAME OF THE MEDICINE

Nepafenac.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in ILEVRO EYE DROPS is Nepafenac 3 mg/mL (0.3%).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ILEVRO is a light yellow to yellow, uniform suspension for multiple-dose topical ophthalmic use.

Nepafenac is a yellow crystalline powder which is poorly soluble in water.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ILEVRO is indicated for the:

-prevention and treatment of postoperative pain and inflammation associated with cataract surgery

-reduction in risk of postoperative macular oedema associated with cataract surgery in patients with non proliferative diabetic retinopathy.

4.2 DOSE AND METHOD OF ADMINISTRATION

For ophthalmic use only.

For individual patient use only.

Shake the bottle well before use. After cap is removed, if a tamper evident snap collar is present and loose, remove before using ILEVRO.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.

For the prevention and treatment of pain and inflammation, the dose is 1 drop of ILEVRO in the conjunctival sac of the affected eye(s) once a day beginning 1 day prior to cataract surgery and continued on the day of surgery. In clinical studies, the effectiveness of ILEVRO was demonstrated for up to 14 days of the postoperative period. Treatment durations greater than two weeks and a

dosing frequency of more than once daily have not been assessed. An additional drop should be administered 30 to 120 minutes prior to surgery.

For the reduction in the risk of postoperative macular oedema associated with cataract surgery in patients with non proliferative diabetic retinopathy, the dose is 1 drop of ILEVRO in the conjunctival sac of the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

Nasolacrimal occlusion and gently closing the eyelid after instillation are recommended. This may reduce the systemic absorption of eye drops and result in a decrease in systemic adverse reactions.

If a dose is missed, one drop should be administered as soon as possible before reverting to the regular dosage routine. Do not use double the amount to make up for the dose that was missed. Using multiple doses may cause unwanted side effects.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance nepafenac or to any of the excipients in ILEVRO.

Hypersensitivity to other nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

Soft contact lenses should not be used with ILEVRO because the benzalkonium chloride preservative may be absorbed by these lenses.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FOR OPHTHALMIC USE – not for oral ingestion.

Patients should be instructed to avoid sunlight during treatment with ILEVRO.

Ocular effects

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of ILEVRO and should be monitored closely for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g. dry eye syndrome), rheumatoid arthritis or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse reactions which may become sight threatening. Topical NSAIDs should be used with caution in these patients. Post-marketing experience with topical NSAIDs also suggest that use more than 24 hours prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemas) in conjunction with ocular surgery. Use ILEVRO with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.

An acute ocular infection may be masked by the topical use of anti-inflammatory medicines. NSAIDs do not have any antimicrobial properties. In case of ocular infection, their use with anti-infectives should be undertaken with care.

Use in hepatic impairment/ renal impairment

ILEVRO has not been studied in patients with hepatic disease or renal impairment. Nepafenac is eliminated primarily through biotransformation and the systemic exposure is very low following topical ocular administration. No dose adjustment is warranted in these patients.

Concomitant therapy

There are very limited data on the concomitant use of prostaglandin analogues and ILEVRO. Considering their mechanisms of action, the concomitant use of these medicinal products is not recommended.

Delayed Healing

Topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Therefore, it is recommended that caution should be exercised if ILEVRO is administered concomitantly with corticosteroids, particularly in patients at high risk for corneal adverse reactions described below.

Contact lenses

Contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, patients should be advised not to wear contact lenses unless clearly indicated by their doctor.

Benzalkonium chloride

ILEVRO contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses.

Soft contact lenses should not be used with ILEVRO because the benzalkonium chloride preservative may be absorbed by these lenses.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since ILEVRO contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

Cross-sensitivity

There is a potential for cross-sensitivity of nepafenac to acetylsalicylic acid, phenylacetic acid derivatives and other NSAIDs.

Paediatric use

The safety and efficacy of ILEVRO in children and adolescents has not been established and its use is not recommended for use in patients under 18 years of age.

Use in the elderly

No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In vitro studies have demonstrated a very low potential for interaction with other medicinal products and protein binding interactions.

Neither nepafenac nor amfenac inhibit any of the major human cytochrome P450 (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) metabolic activities in vitro at concentrations up to 3000 ng/mL. Therefore, interactions involving CYP-mediated metabolism of concomitantly administered medicinal products are unlikely. Interactions mediated by protein binding are also unlikely.

There are very limited data on the concomitant use of prostaglandin analogues and ILEVRO. Considering their mechanisms of action, the concomitant use of these medicinal products is not recommended.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems. Concomitant use of ILEVRO with medications that prolong bleeding time may increase the risk of haemorrhage.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of ILEVRO on human fertility. In male rats, oral dosing of nepafenac decreased sperm motility but did not impair reproductive performance at estimated systemic exposure more than 300 times clinical exposure, based on AUC for nepafenac and amfenac. At similar high exposures in female rats, oral dosing of nepafenac did not impair fertility but did not increase the rate of early resorptions. At the no-effect dose in rat fertility studies (3 mg/kg/day), estimated systemic exposure (AUC) was greater than 80 times clinical exposure.

Use in pregnancy – Pregnancy Category C

ILEVRO should not be used by women of child bearing potential not using contraception.

There are no adequate data regarding the use of nepafenac in pregnant women. Studies in animals have shown nepafenac and/or its metabolites cross the placenta and are associated with reproductive toxicity. In oral reproduction studies performed with nepafenac in rats, there was no evidence of teratogenicity but maternally toxic doses of 10 mg/kg/day or greater were associated with dystocia, increased postimplantation loss, and reduced fetal weights, growth, and survival (systemic exposure more than 800 times clinical exposure, based on total AUC for nepafenac and amfenac). Oral administration of 3 mg/kg/day or greater from early gestation to weaning was associated with maternal mortality around parturition (exposure about 170 times clinical exposure based on AUC), with higher, maternotoxic doses linked to reductions in live births and pup survival and growth. In pregnant rabbits, oral administration of 30 mg/kg/day during organogenesis

produced slight maternotoxicity and a statistically significant increase in the incidence of litter malformations (exposure about 1000 times clinical exposure, based on AUC). The no-effect dose of 10 mg/kg/day was associated with AUC exposure 135 times clinical exposure. The potential risk for humans is unknown.

Since the systemic exposure in non-pregnant women is negligible after treatment with ILEVRO, the risk during pregnancy could be considered low. Nevertheless, as inhibition of prostaglandin synthesis may negatively affect pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development, ILEVRO is not recommended during pregnancy.

Use in lactation

It is unknown whether nepafenac is excreted in human milk. Animal studies have shown excretion of nepafenac and/or its metabolites in the milk of rats. However, no effects on the suckling child are anticipated since the systemic exposure of the breastfeeding woman to nepafenac is negligible. The use of nepafenac or ILEVRO is not recommended during lactation. Also see Section 4.6 Fertility, Pregnancy and Lactation - Use in Pregnancy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events in clinical trials

In clinical studies involving over 1900 patients receiving ILEVRO eye drops, suspension, the most frequently reported adverse reactions were punctate keratitis, keratitis, foreign body sensation in eyes and eye pain which occurred in between 0.4% and 0.1% of patients.

Patients with non proliferative diabetic retinopathy: In the two clinical studies involving 594 patients, patients were exposed to ILEVRO eye drops, suspension treatment for 90 days for the prevention of macular oedema post cataract surgery. The most frequently reported adverse reaction was punctate keratitis which occurred in 1% of patients, resulting in a frequency category of common. The other most frequently reported adverse reactions were keratitis and foreign body sensation in eyes which occurred in 0.5% and 0.3% of patients, respectively both adverse reactions with a frequency category of uncommon.

Additional adverse events have been observed in clinical trials with the use of nepafenac 1 mg/mL eye drops, suspension and may also be observed with the use of ILEVRO.

Description of selected adverse reactions

Clinical trial experience for the long-term use of ILEVRO for the prevention of macular oedema post cataract surgery in patients with non proliferative diabetic retinopathy is limited. Ocular adverse reactions in diabetic patients may occur at a higher frequency than observed in the general population.

Patients with evidence of corneal epithelial breakdown including corneal perforation should immediately discontinue use of ILEVRO and should be monitored closely for corneal health.

Paediatric population: The safety and efficacy of ILEVRO in children and adolescents have not been established.

When nepafenac is prescribed to a patient with non proliferative diabetic retinopathy post cataract surgery to prevent macular oedema, the existence of any additional risk factor should lead to reassessment of the foreseen benefit/risk and to intensify patient monitoring. The safety and efficacy of ILEVRO in patients with proliferative diabetic retinopathy, vitreomacular traction or epiretinal membrane have not been established.

Tabulated list of adverse reactions

The following adverse reactions are classified according to the following convention: 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), or not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ classification	**Adverse reactions**
Immune system disorders	*Rare:* hypersensitivity
Nervous system disorders	*Rare:* dizziness, headache
Eye disorders	*Uncommon*: keratitis, punctate keratitis, corneal epithelium defect, foreign body sensation in eyes, eyelid margin crusting *Rare*: iritis, choroidal effusion, corneal deposits, eye pain, ocular discomfort, dry eye, blepharitis, eye irritation, eye pruritus, eye discharge, allergic conjunctivitis, increased lacrimation, conjunctival hyperaemia
Vascular disorders	*Not known:* blood pressure increased
Gastrointestinal disorders	*Rare:* nausea
Skin and subcutaneous tissue disorders	*Rare:* cutis laxa (dermatochalasis), allergic dermatitis

Post marketing

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse reactions which may become sight threatening.

Additional adverse events have been observed in post marketing experience with the use of nepafenac 1mg/mL eye drops, suspension and may be observed with the use of ILEVRO.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

A topical overdose of ILEVRO may be flushed from the eye(s) with warm tap water. There is no experience of overdose by the ophthalmic route. The application of more than one drop per eye is unlikely to lead to unwanted side-effects.

A bottle of ILEVRO contains 9 mg of nepafenac (3 mg/mL). In a clinical study in which subjects received a single 10 mg oral administration of ^{14}C-nepafenac, no safety concerns based upon a review of adverse events and an assessment of clinical laboratory, cardiovascular and general physical examination parameters were evident. In an acute toxicity study in mice no signs of toxicity were observed after oral administration of nepafenac up to 2000 mg/kg dose (~4400, and ~13,000 times the potential full bottle dose in a child and adult respectively) and in an acute toxicity study in rats animals administered orally with nepafenac at a dose of 100 mg/kg, kg (~220, and ~660 times the potential full bottle dose in a child and adult respectively),survived the observation period of 7 days, swollen abdomens, red exudates on face, little or no stool and less active behavior was seen. Therefore, an oral overdose of ILEVRO is unlikely to result in significant toxicity. However there is no data of the effects of oral overdose in young children or the elderly.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nepafenac is a non-steroidal, anti-inflammatory and analgesic drug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, which is a non-steroidal, anti-inflammatory metabolite. Nepafenac and amfenac inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

In rabbits, nepafenac has been shown to inhibit blood-retinal-barrier breakdown, concomitant with suppression of PGE_2 synthesis. In rabbits, a single topical ocular dose of nepafenac was shown to inhibit prostaglandin synthesis in the iris/ciliary body by up to 89% with inhibition of 36% still present after 30 hours. Ex vivo, PGE_2 synthesis in the retina/choroid was inhibited by 38 – 50% for up to 80 minutes post-dose.

In rabbits, the rate of hydrolytic conversion of nepafenac to amfenac was highest in the retina/choroid followed by the iris/ciliary body and cornea. In human ocular tissues, the highest rate of hydrolytic conversion was in the iris/ciliary body, with lower conversion rates observed in retina/choroid and cornea.

Results from clinical studies indicate that ILEVRO has no significant effect on intraocular pressure.

Clinical trials

Postoperative pain and inflammation

The efficacy and safety of ILEVRO in the prevention and treatment of postoperative pain and inflammation associated with cataract surgery has been demonstrated in two masked, double blind, placebo-controlled clinical trials in which a total of 3462 patients were randomized. Of these, 1339 patients received at least one dose of nepafenac 0.3%. In these studies in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first 14 days of the postoperative period, ILEVRO demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Both studies enrolled patients requiring cataract surgery by phacoemulsification and implantation of a posterior chamber intraocular lens. Patients had no baseline inflammation and did not receive any anti-inflammatory medication other than the assigned therapy. Patients with a history of chronic or recurrent inflammatory eye diseases and patients at increased risk of developing postoperative macular oedema (e.g. diabetic retinopathy patients) in the operative eye were excluded from the study.

Patients treated with ILEVRO were less likely to have ocular pain and measurable signs of inflammation (aqueous cells and flare) in the early postoperative period through to the end of treatment than those treated with its vehicle. In the two studies, ILEVRO cleared inflammation at day 14 post operation in 65% and 68% of patients compared to 25% and 35% of patients on vehicle. Pain free rates in the ILEVRO group were 89% and 91% compared to 40% and 50% of patients on vehicle. The Day 14 results for reduction of both pain and inflammation were statistically significantly superior to the vehicle.

Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients with non proliferative diabetic retinopathy

Two studies in patients with non proliferative diabetic retinopathy were conducted to assess the efficacy and safety of ILEVRO eye drops, suspension dosed once a day for the prevention of postoperative macular oedema associated with cataract surgery.

Clinical study treatment regimen: In these studies, patients were randomized to ILEVRO or Vehicle and had the study drug instilled topically into the eye once daily from Day −1 (the day prior to surgery) through Day 90 (or Early Exit). Separate from the aforementioned study drug administration, subjects also received 1 drop of study drug 30 to 120 minutes prior to the scheduled cataract surgery on Day 0. Regardless of treatment group assignment, all subjects also instilled prednisolone eye drops for 4 weeks postsurgery (4 times daily in the study eye for 2 weeks postsurgery followed by 2 times daily in the study eye for the subsequent 2 weeks postsurgery), beginning with the first postsurgical dosing time point.

Major exclusion criteria: The following specific conditions excluded subjects from participation in the study based on increased background risk of macular oedema: (1) pre-existing macular oedema in the study eye (2) signs of vitreomacular traction or epiretinal membrane.

Efficacy results: In both double-masked, randomised vehicle-controlled studies, conducted in patients with non proliferative diabetic retinopathy, a significantly greater percentage of patients in the vehicle group developed macular oedema (17.3% and 14.3%) compared to patients treated with ILEVRO (2.3% and 5.9%). The corresponding percentages in integrated analysis of the 2 studies were 15.9% in vehicle group and 4.1% in ILEVRO group, p<0.001). A significantly greater percentage of patients achieved improvement of 15 or more letters at Day 14 and maintained the improvement through Day 90 in ILEVRO group (61.7%) compared to vehicle group (43%) in one study; the percentage of subjects was not statistically significant in the 2 treatment groups for this endpoint in the second study (48.8% in ILEVRO group and 50.5% in vehicle group). In integrated analysis of the 2 studies, the percentage of subjects with 15 letter improvement at Day 14 and maintained to Day 90 was higher in ILEVRO group (55.4%) compared to vehicle group (46.7%, p=0.003).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following one drop of ILEVRO in both eyes once daily for four days, low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours post-dose, respectively. The mean steady-state plasma Cmax for nepafenac and for amfenac were 0.847 ± 0.269 ng/mL and 1.13 ± 0.491 ng/mL, respectively, following ocular administration.

Distribution

Amfenac has a high affinity towards serum albumin proteins. *In vitro,* the percentages of amfenac bound to rat albumin, human albumin and human serum are 98.4%, 95.4% and 99.1%, respectively. The binding percentages of nepafenac to plasma proteins for rat, monkey and human are 72.8%, 79.8% and 83.5%, respectively.

Studies in rats have shown that radioactive labelled active substance-related materials distribute widely in the body following single and multiple oral doses of ^{14}C-nepafenac.

Studies in rabbits demonstrated that the topically administered nepafenac is distributed locally from the front of the eye to the posterior segments of the eye (retina and choroid).

Metabolism

Nepafenac undergoes relatively rapid bioactivation to amfenac via intraocular hydrolases.

Subsequently, amfenac undergoes extensive metabolism to more polar metabolites involving hydroxylation of the aromatic ring leading to glucuronide conjugate formation.

Radiochromatographic analyses before and after β-glucuronidase hydrolysis indicated that all metabolites were in the form of glucuronide conjugates, with the exception of amfenac. Amfenac was the major metabolite in plasma, representing approximately 13% of total plasma radioactivity. The second most abundant plasma metabolite was identified as 5-hydroxy nepafenac, representing approximately 9% of total radioactivity at Cmax.

Metabolite profiles of radioactivity in rabbit ocular tissues following a topical dose of 0.3% ^{14}C-AL-6516 showed only AL-6516, AL-6295 and a minor unidentified metabolite.

Excretion

After oral administration of ^{14}C-nepafenac to healthy volunteers, urinary excretion was found to be the major route of radioactive excretions, accounting for approximately 85% while faecal excretion represented approximately 6% of the dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Nepafenac was not mutagenic in bacteria or mammalian cells, but induced chromosomal aberrations in-vitro in Chinese Hamster Ovary cells at concentrations that had precipitate. Nepafenac was not clastogenic in mice in-vivo, even at very high oral doses (5000 mg/kg). The weight of evidence indicates a low genotoxic potential for nepafenac.

Carcinogenicity

Nepafenac has not been evaluated in long-term carcinogenicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ILEVRO also contains boric acid, propylene glycol, carbomer 974P, sodium chloride, guar galactomannan, carmellose sodium, disodium edetate, hydrochloric acid and/or sodium hydroxide (to adjust pH), water-purified and benzalkonium chloride (0.05 mg/mL) as preservative.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store ILEVRO below 25^{o}C. Protect from light.

Discard 4 weeks after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

4 mL round or oval white (opaque) low density polyethylene (LDPE) bottles with a LDPE dispensing plug and white polypropylene screw cap (DROP-TAINER®) containing 3 mL eye drops suspension. The bottle may be presented in a pouch.

Consumer Medicine Information is supplied with this product.

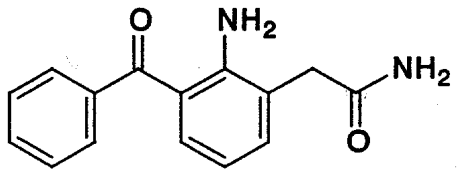
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of nepafenac is represented below:



The pH of ILEVRO is approximately 6.8.

Chemical Name(s)

2-Amino-3-benzoylbenzeneacetamide

2-(2-Amino-3-benzoylphenyl) acetamide

Empirical Formula

$C_{15}H_{14}N_2O_2$

Molecular Weight

254.28

CAS number

78281-72-8.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

1800 671 203

http://www.novartis.com.au

9 DATE OF FIRST APPROVAL

4 November 2015

10 DATE OF REVISION

30 August 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2.4	Minor rewording for the tamper evident snap collar reference
6.5	Oval bottle presentation added to PI.

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