PRODUCT INFORMATION – ARCATUS® (TRIAMCINOLONE ACETONIDE SUSPENSION FOR INJECTION)

1 NAME OF THE MEDICINE

Triamcinolone acetonide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the sterile, aqueous suspension contains 40 mg of triamcinolone acetonide.

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

3 PHARMACEUTICAL FORM

ARCATUS® is provided as a suspension for injection in a single-dose glass vial with a rubber stopper and an aluminum seal. The SCS Microinjector™ is a piston syringe and a needle approximately 1 mm in length (900 µm and 1100 µm needles are included) for conducting the suprachoroidal injection. The suspension is white to off-white suspension with no visible foreign particulate matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ARCATUS® is indicated for the treatment of macular oedema associated with non-infectious uveitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

The recommended dose of ARCATUS® is 4 mg (0.1 mL of the 40 mg/mL suspension for injection) to the affected eye.

There is currently no experience of repeat administrations beyond two suprachoroidal injections administered 12 weeks apart.

ARCATUS® must be administered by a qualified ophthalmologist experienced in SCS injections.

Method of administration

For suprachoroidal injection using the SCS Microinjector™.

Preparation for Administration

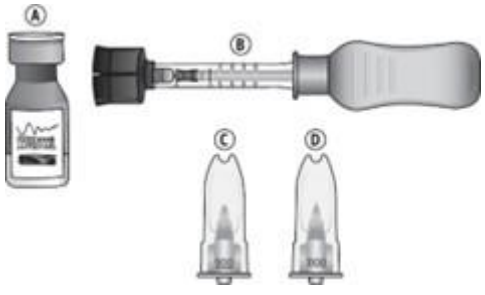
Suprachoroidal injection is performed under aseptic conditions. The components for administration include:

A. One single-dose glass vial of triamcinolone acetonide suspension for injection 40 mg/mL

B. One SCS Microinjector™ syringe with vial adapter attached

C. One 30-G x 900-µm needle

D. One 30-G x 1100-µm needle



Step 1

Figure A

Remove the tray from the carton (see Figure A).
The tray consists of two compartments:
• An open non-sterile compartment that holds the vial
• A sealed compartment that contains a sterile tray

Step 2

Figure B

Examine the tray for damage (see Figure B). Ensure that the sealed compartment cover is intact and that there is no evidence of damage. If damage is present, do not use.

Step 3

Figure C

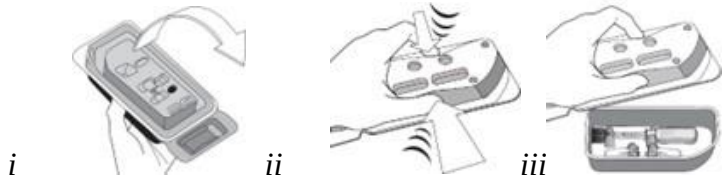
Remove the vial from the tray (see Figure C). Examine the vial and ensure there is no evidence of damage. Set aside for use in step 6.

Step 4

Figure D

Peel off the compartment cover, exposing the sterile tray (see Figure D).

Step 5



i *ii* *iii*

Figure E

Grasp and hold the long sides of the tray and invert the tray. Squeeze gently to release the sterile tray onto the appropriate sterile preparation surface (see Figure E, i – iii).

Step 6

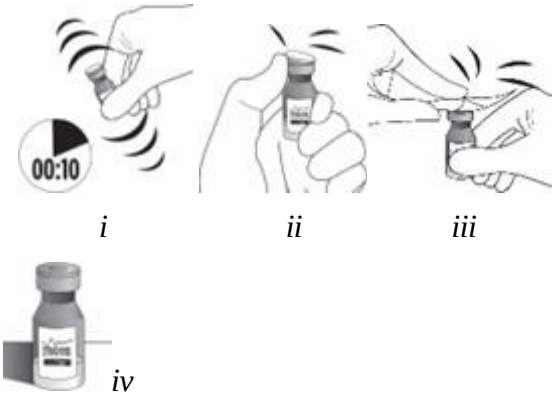


Figure F

Vigorously shake the vial for 10 seconds. Inspect the vial for clumping or granular appearance of the sterile contents. If clumping or granular appearance is present, do not use. Remove the protective plastic cap from the vial and clean the top of the vial with an alcohol wipe. Place the vial on a flat surface (see Figure F, i – iv). To avoid settling of the suspension, continue to the next steps without delay.

Step 7

Figure G

Remove the syringe with attached vial adapter from the tray (see Figure G). Ensure the vial adapter is secured to the syringe by tightening the connection.

Step 8

Figure H

Holding the clear barrel of the syringe, connect the vial adapter to the vial by firmly pushing the spike of the vial adapter straight through the center of the vial septum until it snaps securely into place (see Figure H).
NOTE: Do not introduce additional air into the syringe prior to connecting the vial adapter to the vial.

Step 9

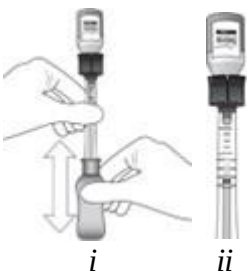


Figure I

Invert the entire assembly so that the vial is directly above the syringe. Slide the white plunger handle all the way back and forth multiple times to fill the entire syringe with drug and remove any remaining air (see Figure I, i and ii).
NOTE: The syringe should be handled by the clear barrel during filling, connecting and disconnecting procedures. The white plunger handle has a stop to prevent complete removal of the plunger from the syringe.

Step 10

Figure J

While holding the vial adapter and vial, disconnect the syringe by twisting it off of the adapter (see Figure J).
Retain the vial, with the vial adapter connected, in the event re-access is necessary.

Step 11

Figure K

Connect the 900-µm needle to the syringe by twisting onto the syringe (see Figure K). At the discretion of the physician, the longer needle may be used. Ensure a secure connection.

Step 12

Figure L

Hold the syringe barrel with the needle pointing up. Expel air bubbles and excess drug by slowly sliding the white plunger handle so that the plunger tip aligns with the line that marks 0.1 mL on the syringe (see Figure L).
NOTE: Perform the suprachoroidal injection without delay to prevent settling of the drug.

2.3 Administration

The suprachoroidal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent), and a sterile cotton swab. Adequate anesthesia and a broad-spectrum microbicide applied to the periocular skin, eyelid, and ocular surface are recommended to be given prior to the suprachoroidal injection.

Step 13

Figure M

Identify the injection site by measuring 4 – 4.5 mm posterior to the limbus using the tip of the needle cap or ophthalmic calipers (see Figure M).

Step 14

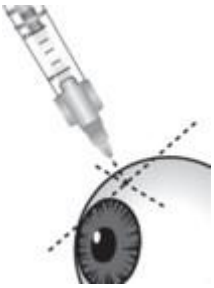


Figure N

Carefully pull off the needle cap to expose the needle. Holding the syringe perpendicular to the ocular surface, insert the needle through the conjunctiva into the sclera (see Figure N).

Step 15

Figure O

Once the needle is inserted into the sclera, ensure that the hub of the needle is in firm contact with the conjunctiva, compressing the sclera and creating a dimple on the ocular surface using a light amount of force against the eye. Maintain the dimple and perpendicular positioning throughout the injection procedure (see Figure O).

Step 16

Figure P

While maintaining the dimple on the ocular surface, gently press the white plunger handle so that the plunger moves forward and drug is slowly injected over 5 – 10 seconds. Movement of the plunger will be felt as a loss of resistance and indicates that the needle is in the correct anatomical location for suprachoroidal injection (see Figure P).

If resistance is felt and the plunger does not advance, confirm the hub is in firm contact with the conjunctiva creating a dimple and that the syringe is positioned perpendicular to the ocular surface. Small adjustments in positioning may be necessary.

Step 17

Maintain the hub against the eye for 3 – 5 seconds after the drug product has been injected.

Step 18

Remove the needle slowly from the eye while holding a sterile cotton swab next to the needle as it is withdrawn. Immediately cover the injection site with a sterile cotton swab.

Step 19

Hold the swab over the injection site with light pressure for a few seconds and then remove.

If continued resistance is experienced during injection attempts:

- Remove the needle from the eye and examine the eye for any issues. If patient safety is not at risk, the physician may use medical judgment to restart the injection procedure at a new site adjacent to the original injection site.
- If resistance continues and patient safety is not at risk, the physician may use appropriate medical judgment to change to the additional included needle in the sterile tray. Twist to remove the needle and reconnect the syringe to the vial by twisting the syringe onto the vial adapter. Repeat the preparation and injection process as stated in steps 9 – 18 with the additional needle (allowing for any partial dose given with the first needle when completing preparation Step 12).

Immediately following suprachoroidal injection, patients should be monitored for elevation of intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following suprachoroidal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of eye, photophobia, blurring of vision) without delay.

Each ARCATUS® package (microinjector syringe with vial adapter, 900-µm needle, 1100-µm needle, and vial of triamcinolone acetonide suspension for injection 40 mg/mL) is single-dose and should only be used for the treatment of one eye.

After suprachoroidal injection, all drug product and components (used or unused) must be discarded appropriately.

4.3 CONTRAINDICATIONS

Ocular or Periocular Infections

ARCATUS® is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Hypersensitivity

ARCATUS® is contraindicated in patients with known hypersensitivity to triamcinolone acetonide or any other components of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The safety and efficacy of ARCATUS® administered to both eyes concurrently have not been studied. Administration to both eyes concurrently is not recommended.

Potential Corticosteroid-Related Effects

Use of corticosteroids may produce cataracts, increased intraocular pressure, and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex.

Corticosteroids should not be used in patients with active ocular herpes simplex.

Alterations in Endocrine Function

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia can occur following administration of a corticosteroid. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Use in the elderly

No overall differences in safety or effectiveness have been observed between elderly and younger patients following ARCATUS® administration.

Paediatric use

Safety and effectiveness of ARCATUS® in pediatric patients have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No data available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No information is available on the effect of triamcinolone acetonide on fertility.

Use in pregnancy

Risk Summary

There are no adequate and well-controlled studies with ARCATUS® in pregnant women to inform drug-associated risks. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids has been shown to produce teratogenicity at clinically relevant doses. There is negligible systemic ARCATUS® exposure following suprachoroidal injection [see Pharmacokinetic Properties (5.2)]. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Animal reproduction studies using ARCATUS® have not been conducted. In animal reproductive studies from the published literature, topical ocular administration of corticosteroids to pregnant mice and rabbits during organogenesis has been shown to produce cleft palate, embryofetal death, herniated abdominal viscera, hypoplastic kidneys and craniofacial malformations.

Use in lactation

Risk Summary

It is not known whether ocular administration of corticosteroids could result in sufficient systemic

absorption to produce detectable quantities in human milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARCATUS® and any potential adverse effects on the breastfed infant from ARCATUS®. There are no data on the effects of ARCATUS® on milk production.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ARCATUS® was studied in a multicenter, randomized, sham-controlled, double-masked study in patients with macular oedema associated with uveitis. Table 1 summarizes data available from the clinical trial for ARCATUS® treated patients and control patients.

The most common ocular (study eye) adverse reactions occurring in ≥ 2% of patients and non-ocular adverse reactions occurring in ≥ 5% of patients are shown in Table 1.

Table 1: Ocular Adverse Reactions Reported in ≥ 2% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

Adverse Reaction	ARCATUS® (N = 96) n (%)	Control (N = 64) n (%)
Ocular		
Increased intraocular pressure, non-acute [a, b]	13 (14%)	9 (14%)
Eye pain, non-acute [a]	11 (12%)	0
Cataract [c]	7 (7%)	4 (6%)
Increased intraocular pressure, acute [a,d]	6 (6%)	0
Vitreous detachment	5 (5%)	1 (2%)
Injection site pain	4 (4%)	2 (3%)
Conjunctival haemorrhage	4 (4%)	2 (3%)
Visual acuity reduced	4 (4%)	1 (2%)
Dry eye	3 (3%)	1 (2%)
Eye pain, acute [d]	3 (3%)	0
Photophobia	3 (3%)	0
Vitreous floaters	3 (3%)	0
Uveitis	2 (2%)	7 (11%)
Conjunctival hyperaemia	2 (2%)	2 (3%)
Punctate keratitis	2 (2%)	1 (2%)
Conjunctival oedema	2 (2%)	0
Meibomianitis	2 (2%)	0
Anterior capsule contraction	2 (2%)	0
Chalazion	2 (2%)	0

Eye irritation	2 (2%)	0
Eye pruritus	2 (2%)	0
Eyelid ptosis	2 (2%)	0
Photopsia	2 (2%)	0
Vision blurred	2 (2%)	0
Non-ocular		
Headache	5 (5%)	2 (3%)

[a] Includes intraocular pressure increased and ocular hypertension
[b] Defined as not occurring on the day of the injection procedure, or occurring on the day of the injection procedure and not resolving the same day
[c] Includes cataract, cataract cortical, and cataract subcapsular
[d] Defined as occurring on the day of the injection procedure and resolving the same day

4.9 OVERDOSE

There is no specific treatment for overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Triamcinolone acetonide is a synthetic glucocorticoid (glucocorticoids are often referred to as corticosteroids) with immunosuppressive and anti-inflammatory activity. The primary mechanism of action for triamcinolone acetonide is as a corticosteroid hormone receptor agonist.

Clinical trials

The efficacy of ARCATUS® was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled study in patients with macular edema associated with anterior-, intermediate-, posterior-, or pan-uveitis. Patients were treated at baseline and week 12.

The primary efficacy endpoint was the proportion of patients in whom best corrected visual acuity (BCVA) had improved by ≥ 15 letters from baseline after 24 weeks of follow-up (Table 2).

Table 2: Number of Patients with ≥ 15 Letters Improvement from Baseline at Week 24

Patients Who Gained ≥ 15 Letters from Baseline at Week 24	**ARCATUS® (N = 96)**	**Control (N = 64)**
n (%)	45 (47%)	10 (16%)
Estimated Difference (95% CI)	31% (15%, 46%)	
CMH p-value*	< 0.01	

* The p-value was based on a Cochran Mantel Haenszel test for general association between treatment and response with stratification by country.

A statistically significantly greater proportion of patients treated with ARCATUS® achieved a ≥ 15-letter improvement in BCVA than control patients (p< 0.01) at Week 24.

BCVA mean change from baseline at different visits is shown in Figure 1. Central subfield retinal thickness (CST) mean change from baseline at different visits is shown in Figure 2.

Figure 1: Mean Change from Baseline in BCVA

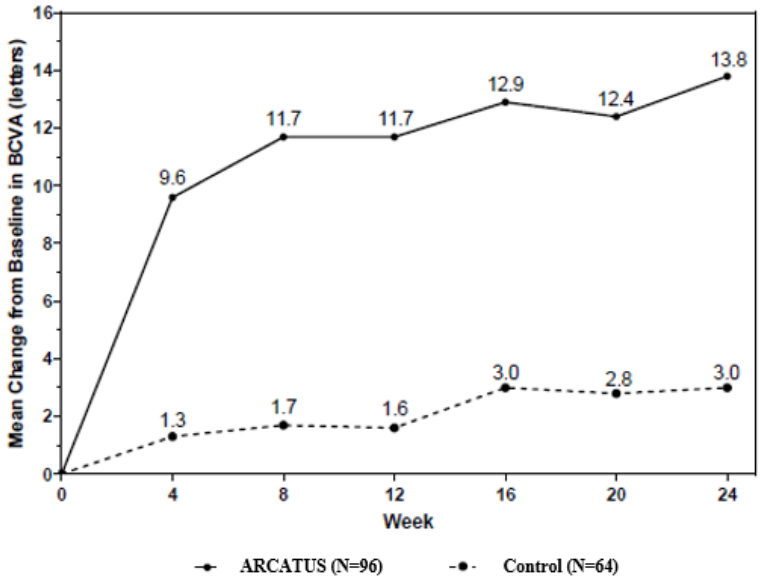
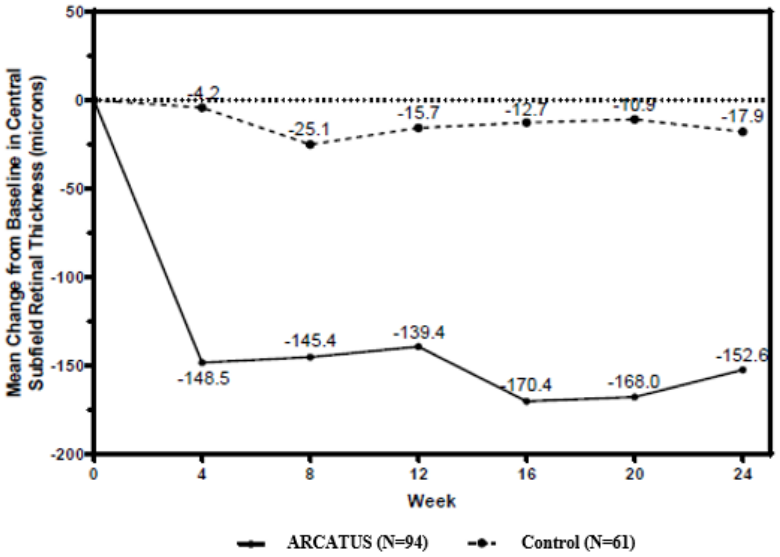


Figure 2: Mean Change from Baseline in CST



5.2 PHARMACOKINETIC PROPERTIES

In animal studies, data demonstrated that suprachoroidal injections resulted in larger amounts in total of triamcinolone acetonide found in the sclera, choroid, retinal pigment epithelial and retina, than with intravitreal injections of triamcinolone acetonide. Lower amounts of triamcinolone acetonide were found in the anterior segment and lens as compared to intravitreal injections of triamcinolone acetonide.

Plasma triamcinolone acetonide concentrations were evaluated in 19 patients with dosing of 4 mg ARCATUS® at Day 0 and Week 12. Plasma triamcinolone acetonide concentrations in all 19 patients were below 100 pg/mL at Week 4, 12, and 24 (concentrations ranged from < 10 pg/mL [LLOQ (lower limit of quantitation) of the assay] to 88.9 pg/mL), with the exception of one patient with a value of 243.4 pg/mL prior to the second dose at Week 12.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No information is available on the genotoxicity potential of triamcinolone acetonide.

Carcinogenicity

No information is available on the carcinogenic potential of triamcinolone acetonide.

Mutagenesis

No information is available on the mutagenic potential of triamcinolone acetonide.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each mL of the sterile aqueous suspension contains the following excipients: 0.55% (weight/volume [w/v]) sodium chloride, 0.5% (w/v) carboxymethylcellulose sodium, and 0.02% (w/v) polysorbate 80. It also contains potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, sodium acetate trihydrate, sodium citrate dihydrate, and water for injections. Hydrochloric acid may be used to

adjust pH to a target value of 6.5.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Please refer to expiry date on the outer carton.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C (Do not freeze and refrigerate). The drug vial should be protected from light by storing in the carton. Discard residue.

6.5 NATURE AND CONTENTS OF CONTAINER

ARCATUS® is supplied with the following sterile components for administration, sealed in a Tyvek covered tray, and one single-dose glass vial, in a carton with a package insert:

- One SCS Microinjector™ syringe with vial adapter attached
- One 30-G x 900-µm needle
- One 30-G x 1100-µm needle
- One single-dose vial of triamcinolone acetonide suspension for injection 40 mg/mL

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

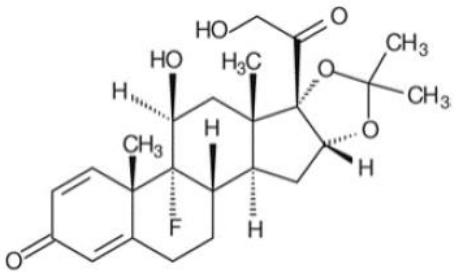
Any unused medicine or waste material should be disposed.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

The chemical name for triamcinolone acetonide is 9-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its chemical structure is:



Molecular weight 434.50 g/mol; molecular formula $C_{24}H_{31}FO_6$

CAS number: 76-25-5

7 PRODUCT REGISTRANT

ARCTIC VISION SINGAPORE PTE. LTD.
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SOUTH BEACH TOWER,
SINGAPORE (189767)

8 DATE OF FIRST APPROVAL

9 DATE OF REVISION

Summary table of changes

Section changed	***Summary of new information***