1. NAME OF THE MEDICINAL PRODUCT

GLANATEC ophthalmic solution 0.4% w/v

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the ophthalmic solution contains 4.896 mg of ripasudil hydrochloride hydrate equivalent to 4.0 mg of ripasudil.
Each bottle of 5 mL of the ophthalmic solution contains 24.48 mg of ripasudil hydrochloride hydrate equivalent to 20.0 mg of ripasudil.

Excipients with known effect
Each mL of the ophthalmic solution contains 0.04 mg of benzalkonium chloride concentrated solution 50.

For a full list of excipients see Section 6.1.

3. PHARMACEUTICAL FORM

Sterile aqueous ophthalmic solution
Colorless to clear light yellow
pH 5.0 to 7.0
Osmotic pressure ratio of approximately 1 (ratio to isotonic sodium chloride solution)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLANATEC is indicated to decrease elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma as adjunctive therapy in patients who are insufficiently responsive to topical beta-blockers or prostaglandin analogues, or as monotherapy in patients who are intolerant or contraindicated to other intraocular pressure lowering medications.

4.2 Posology and method of administration

Posology
Use in adults, including the elderly
Instill one drop into the affected eye(s) twice daily.

Use in paediatric population
Safety in low birth weight infants, newborns, infants, and children has not been established.

Method of Administration
(1) Route of administration: Instillation only.
(2) When dispensing the drug: Instruct patients on the following:
1) In the instillation, the patient should tilt the head backwards, open the affected eye, instill the drug into the conjunctival sac, close the eyelid for 1 to 5 minutes while compressing the lacrimal part, and open the eye.
2) Be careful during the instillation to avoid direct contact of the tip of the container with the eye in order to prevent contamination of the drug.
3) Instill with an interval of at least 5 minutes when using the drug in combination with other ophthalmic solutions.

4.3 Contraindications

GLANATEC is contraindicated in patients with history of hypersensitivity to any of the components of GLANATEC (see Section 6.1)

4.4 Special warnings and precautions for use

Acute primary angle-closure glaucoma
Consider treatments other than drug therapy, such as surgical therapy, when using GLANATEC for acute primary angle-closure glaucoma.

Conjunctival hyperaemia
In clinical studies, conjunctival hyperaemia in association with the use of ripasudil has been reported. The event usually occurs transiently at the time of instillation, but be cautious if it continues. Take any appropriate measures such as discontinuation of treatment if this event occurs.

Conjunctivitis (including conjunctivitis allergic) and blepharitis (including allergic blepharitis)
In clinical studies, conjunctivitis (including conjunctivitis allergic) and blepharitis (including allergic blepharitis) have been reported in association with the use of ripasudil. The incidence of conjunctivitis allergic and blepharitis allergic tends to be high in patients with long-term instillation. Take any appropriate measures such as discontinuation of treatment if these events occur.

Other adverse reactions
The adverse reactions listed in Section 4.8 “Undesirable effects” were observed in clinical studies. Take any appropriate measures such as discontinuation of treatment if these events occur.

Contact lenses
GLANATEC has not been studied in patients wearing contact lenses. The preservative in GLANATEC, benzalkonium chloride may be adsorbed by the soft contact lens. Patients must be instructed to remove contact lenses prior to the application of GLANATEC and wait at least 15 minutes after instillation of the dose before reinsertion.

Use in paediatric population
Safety in low birth weight infants, newborns, infants, and children has not been established (there is no use experience).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy, and lactation

Pregnancy
The safety of GLANATEC has not been established in pregnant women. GLANATEC should be used in pregnant women or possibly pregnant women only when therapeutic benefits are deemed to outweigh potential risks.

Breastfeeding
Animal studies (rats, oral administration) have shown that the drug was secreted in breast milk. Do not instill GLANATEC in breastfeeding women. If use of GLANATEC is unavoidable, breastfeeding should be suspended.

Fertility
No current data.

4.7 Effects on ability to drive and use machines

No findings suggesting that GLANATEC affects the ability to drive or operate machinery or impairment of mental ability were obtained during the development phase of GLANATEC.

4.8 Undesirable effects

Summary of the safety profile
In clinical studies, 500 out of 662 subjects (75.5%) experienced adverse reactions. The main adverse reactions included conjunctival hyperaemia in 457 subjects (69.0%), conjunctivitis (including conjunctivitis allergic) in 71 subjects (10.7%), and blepharitis (including allergic blepharitis) in 68 subjects (10.3%).

Summary of adverse reactions
Adverse reactions and frequencies observed in clinical studies are listed below by body site or by mechanism of onset of events.

	≥ 5%	≥ 0.1% and < 5%
Eye	Conjunctival hyperaemia, conjunctivitis (including conjunctivitis allergic), blepharitis (including allergic blepharitis), eye irritation	Corneal epithelial disorder (such as corneal erosion and punctate keratitis), eye pruritus, abnormal sensation in eye, eye discharge, eye pain, conjunctival follicles, intraocular pressure increased
Hypersensitivity		Rash, erythema

Corneal thickness tended to decrease in clinical studies. Decreases in corneal thickness caused by instillation of GLANATEC were reversible.

Postmarketing experience
Following adverse reactions have been reported, but the incidence of events cannot be calculated and are unknown because these events include the events reported as spontaneous reports.

	Incidence unknown
Eye	Eyelid oedema, vision blurred
Hypersensitivity	Contact dermatitis

4.9 Overdose

No overdoses were observed during the development phase of GLANATEC. A topical overdose is not likely to occur or to be associated with toxicity. If overdose with GLANATEC occurs, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics
ATC Code: Not yet assigned.

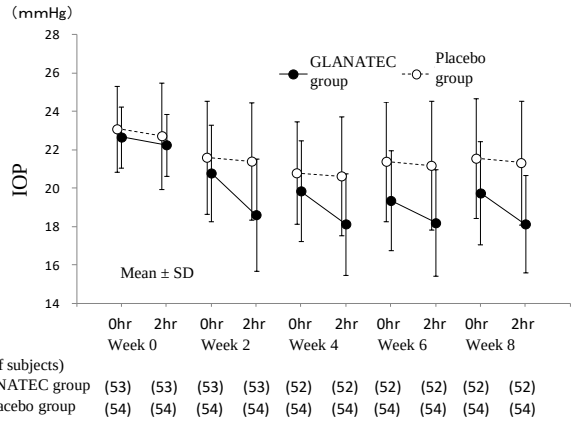
Mechanism of Action
Inhibition of Rho kinase to facilitate aqueous outflow from the conventional outflow pathway via the trabecular meshwork and Schlemm's canal has been suggested as the IOP-lowering mechanism of action by ripasudil.
(1) Ripasudil selectively inhibited human ROCK-1 and ROCK-2, which are isoforms of Rho kinases (*in vitro*).

(2) After a single instillation of GLANATEC to rabbits, the aqueous outflow rate was significantly increased compared to the group treated with the vehicle.
(3) A single instillation of GLANATEC to rabbits did not affect the volume of uveoscleral outflow or aqueous production.

Pharmacodynamic Effects
After a single instillation of ripasudil hydrochloride hydrate ophthalmic solution at 0.0625% to 0.5% to rabbits and the same solution at 0.1% to 0.4% to monkeys, a concentration-dependent IOP-lowering effect was observed.

Clinical efficacy
Phase 3 Placebo-controlled Double-masked Comparative Study
In Japanese patients with primary open-angle glaucoma or ocular hypertension, placebo or GLANATEC was instilled at 1 drop/eye dose in both eyes twice daily for 8 weeks. Changes in IOP over time and the amount of change in IOP are shown in Figure 1 and Table 1. The study demonstrated a significant IOP-lowering effect in the GLANATEC group compared with the placebo group.

Figure 1. Changes in IOP Over Time After Monotherapy



Horizontal axis: 0 hr= immediately before instillation, 2 hr= 2 hours after instillation
(at Week 0, 0 hr= 9:00 am, 2 hr= 11:00 am)

Table 1. Changes in IOP (mmHg) After Monotherapy

	Immediately before morning instillation	2 hours after instillation
GLANATEC group (n=52)	-2.865±0.289 [-3.439, -2.292]	-3.962±0.284 [-4.525, -3.398]
Placebo group (n=54)	-1.843±0.284 [-2.405, -1.280]	-1.679±0.279 [-2.232, -1.126]
Difference between groups	-1.023±0.405* [-1.826, -0.219]	-2.283±0.398** [-3.072, -1.493]

Least-square mean ± SE, [95% confidence interval]
Primary endpoint: Amount of changes in IOP at 3 timepoints (weeks 4, 6, and 8) from week 0.
Primary analysis: Repeated measures ANOVA at 3 timepoints. Multiplicity between the timepoints (immediately before morning instillation, 2 hours after instillation) is adjusted by treating it by product propositions.
*p≤0.05, **p≤0.01

Phase 3 Combination Study with Latanoprost Ophthalmic Solution
In Japanese patients with primary open-angle glaucoma or ocular hypertension in whom latanoprost ophthalmic solution 0.005% was not adequately effective, placebo or GLANATEC was instilled at 1 drop/eye dose in both eyes twice daily in addition to latanoprost ophthalmic solution 0.005% for 8 weeks. Changes in IOP over time and the amount of change in IOP are shown in Figure 2 and Table 2.

Figure 2. Changes in IOP Over Time During Use in Combination with Latanoprost Ophthalmic Solution

Horizontal axis: 0 hr = immediately before instillation, 2 hr = 2 hours after instillation (at Week 0, 0 hr = 9:00 am, 2 hr = 11:00 am)

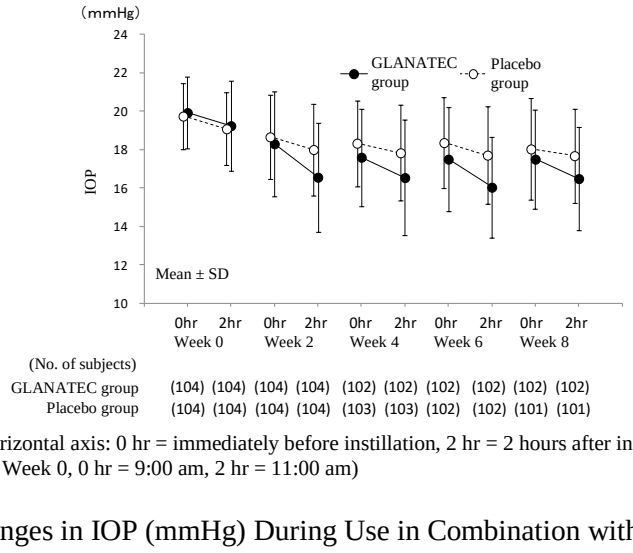
Table 2. Changes in IOP (mmHg) During Use in Combination with Latanoprost Ophthalmic Solution

	Immediately before morning instillation	2 hours after instillation
GLANATEC group (n=101)	-2.246±0.164 [-2.569, -1.922]	-3.191±0.178 [-3.543, -2.840]
Placebo group (n=102)	-1.808±0.163 [-2.129, -1.486]	-1.835±0.177 [-2.184, -1.486]
Difference between groups	-0.438±0.231 [-0.894, 0.018]	-1.356±0.251** [-1.852, -0.861]

Least-square mean ± SE, [95% confidence interval]
Primary endpoint: Amount of changes in IOP at 3 timepoints (weeks 4, 6, and 8) from week 0.
Primary analysis: Repeated measures ANOVA at 3 timepoints. Multiplicity between the timepoints (immediately before morning instillation, 2 hours after instillation) is adjusted by treating it by product propositions.
**p≤0.01

Phase 3 Combination Study with Timolol Ophthalmic Solution
In Japanese patients with primary open-angle glaucoma or ocular hypertension in whom timolol maleate ophthalmic solution 0.5% was not adequately effective, placebo or GLANATEC was instilled at 1 drop/eye dose in both eyes twice daily in addition to timolol maleate ophthalmic solution 0.5% for 8 weeks. Changes in IOP over time and the amount of change in IOP are shown in Figure 3 and Table 3. The study demonstrated a significant IOP-lowering effect in the GLANATEC group compared with the placebo group.

Figure 3. Changes in IOP Over Time During Use in Combination with Timolol Maleate Ophthalmic Solution



Horizontal axis: 0 hr = immediately before instillation, 2 hr = 2 hours after instillation
(at Week 0, 0 hr = 9:00 am, 2 hr = 11:00 am)

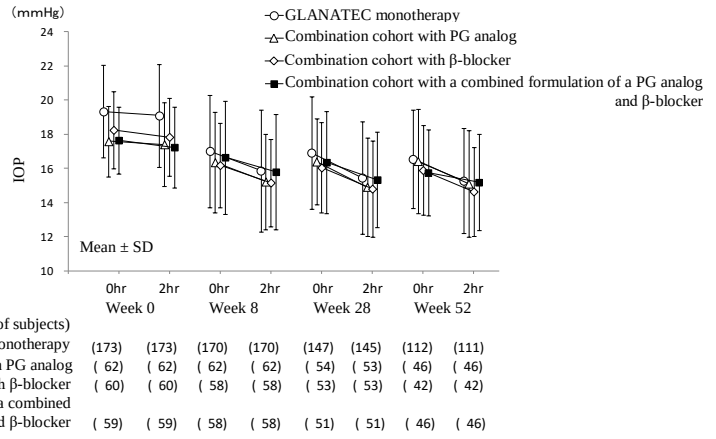
Table 3. Changes in IOP (mmHg) During Use in Combination with Timolol Maleate Ophthalmic Solution

	Immediately before morning instillation	2 hours after instillation
GLANATEC group (n=102)	-2.382±0.161 [-2.700, -2.065]	-2.881±0.172 [-3.220, -2.541]
Placebo group (n=103)	-1.485±0.161 [-1.802, -1.169]	-1.301±0.171 [-1.639, -0.963]
Difference between groups	-0.897±0.228** [-1.345, -0.448]	-1.580±0.243** [-2.059, -1.101]

Least-square mean ± SE, [95% confidence interval]
Primary endpoint: Amount of changes in IOP at 3 timepoints (weeks 4, 6, and 8) from week 0.
Primary analysis: Repeated measures ANOVA at 3 timepoints. Multiplicity between the timepoints (immediately before morning instillation, 2 hours after instillation) is adjusted by treating it by product propositions.
**p≤0.01

Phase 3 Long-term Study
In Japanese patients with primary open-angle glaucoma, exfoliation glaucoma, or ocular hypertension, GLANATEC was instilled at 1 drop/eye dose in both eyes twice daily for 52 weeks, either alone or in addition to prostaglandin (PG) analogs, β-blockers, or combination drugs containing them. Changes in IOP over time are shown in Figure 4. The study demonstrated a stable IOP-lowering effect in long-term instillation of GLANATEC and did not show attenuation of the IOP-lowering effect owing to the prolongation of the treatment period, either as monotherapy or in combination therapy.

Figure 4. Changes in IOP Over Time in Long-term Instillation



Horizontal axis: 0 hr = immediately before instillation, 2 hr = 2 hours after instillation (at Week 0, 0 hr = 9:00 am, 2 hr = 11:00 am)

5.2 Pharmacokinetic properties

Plasma Concentration and Urinary Excretion
GLANATEC was instilled repeatedly to healthy Japanese male adults at 1 drop/eye dose in both eyes twice daily for 7 days, and the changes of ripasudil and its main metabolite M1 (isoquinoline ring position 1 hydroxylated form) over time in plasma concentrations and their pharmacokinetic parameters are shown in Figure 5 and Table 4. The entry of ripasudil into the systemic circulation and the elimination thereof from the body were rapid. In addition, most of ripasudil and M1 were excreted in the urine by 12 hours after completion of repeated instillation.

Figure 5. Changes Over Time in Plasma Concentration After Repeated Instillation in Healthy Male Adults

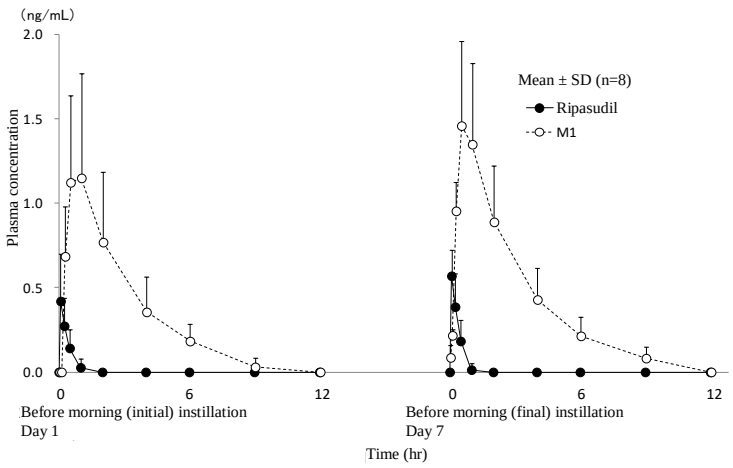


Table 4. Plasma Pharmacokinetic Parameters After Repeated Instillation in Healthy Male Adults

		t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·hr/mL)	$t_{1/2}$ (hr)
Ripasudil	Day 1	0.083 [0.0] n=7	0.420±0.278 n=8	0.183±0.135 n=8	-
	Day 7	0.083 [56.6] n=8	0.622±0.161 n=8	0.231±0.091 n=8	0.455 n=1
M1	Day 1	0.500 [37.6] n=8	1.198±0.582 n=8	3.838±2.085 n=8	-
	Day 7	0.500 [31.4] n=8	1.465±0.504 n=8	4.761±1.869 n=8	2.189±0.465 n=8

Mean ± SD, except t_{max}, for which the median (coefficient of variation (%)) is shown.

Entry into the Ocular Tissues

After a single dose of GLANATEC (50 μL) was instilled to both eyes of pigmented rabbits, the drug in the cornea and the aqueous humor reached the maximum concentration (68135.4 ng/g and 4126.39 ng/mL, respectively) by 0.25 hour and then was rapidly eliminated. In the lens, the drug reached the maximum concentration (154.37 ng/g) by 0.5 hour and then was slowly eliminated.

After a single dose of ^{14}C-ripasudil hydrochloride ophthalmic solution 1.0% (50 μL) was instilled to pigmented rabbits, the drug rapidly entered each ocular tissue. In the ocular tissues, a high radioactivity concentration was detected particularly in the iris/ciliary body and the retina/choroid, which are tissues containing melanin. After instillation twice daily for 7 days, the radioactivity concentration in the tissues containing melanin was obviously higher than after the single-dose instillation, and the radioactivity concentration tended to disappear gradually in all tissues.

5.3 Preclinical safety data

In the 2.0% (twice daily) group in the 13-week repeated instillation study in rabbits and the 4.0% (4 times daily) group in the 13-week repeated instillation study in dogs, irreversible degeneration of lens fibers with opacification was observed in the suture line of the anterior lens. Such changes in the lens are thought to have been caused by the inhibition of formation of actin stress fibers by the Rho kinase inhibiting effect of GLANATEC, which led to the inhibition of differentiation into the fiber cells of the lens and subsequent extension and migration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous sodium dihydrogen phosphate, glycerin, sodium hydroxide, benzalkonium chloride concentrated solution 50, purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

Discard four weeks after first opening.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

A polypropylene bottle containing ultraviolet-absorbing agent with a low-density polyethylene inner plug and a polypropylene cap containing 5 mL ophthalmic solution. A carton contains 1 bottle.

7. PRODUCT OWNER

Name : KOWA COMPANY, LTD.
Address : 6-29, Nishiki 3-chome, Naka-ku, Nagoya, Aichi, JAPAN

8. REGISTRATION NUMBER

XXXXXXXXXXXX

9. DATE OF REVISION OF THE TEXT

January 2020