Report on Deliberation Results

September 14, 2016
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Mikeluna Combination Ophthalmic Solution
Non-proprietary Name	Carteolol Hydrochloride/Latanoprost (JAN)*
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015

Results of Deliberation

In its meeting held on September 7, 2016, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is six years, the drug product is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 15, 2016
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Mikeluna Combination Ophthalmic Solution
Non-proprietary Name	Carteolol Hydrochloride/Latanoprost
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015
Dosage Form/Strength	Ophthalmic solution containing 20 mg of carteolol hydrochloride and 50 μg of latanoprost per mL
Application Classification	Prescription drug, (2) New combination drug(s)
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug 3

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data submitted demonstrate the efficacy of the product in the treatment of glaucoma and ocular hypertension and acceptable safety in view of the benefits indicated by the data submitted, as shown in Attachment.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication	Glaucoma and ocular hypertension
Dosage and Administration	The dosage is one drop of Mikeluna once daily.
Conditions of Approval	The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 9, 2016

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Mikeluna Combination Ophthalmic Solution
Non-proprietary Name	Carteolol Hydrochloride/Latanoprost
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015
Dosage Form/Strength	Ophthalmic solution containing 20 mg of carteolol hydrochloride and 50 μg of latanoprost per mL
Proposed Indication	Glaucoma and ocular hypertension
Proposed Dosage and Administration	The dosage is one drop of Mikeluna once daily.

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List of Abbreviations

AUC	Area under the concentration-time curve
C_{max}	Maximum concentration
CAR	Mikelan LA ophthalmic solution 2% (containing 2% carteolol hydrochloride)
CI	Confidence interval
CTD	Common technical document
FAS	Full analysis set
GC	Gas chromatography
GCP	Good clinical practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH Q1E Guideline	"Evaluation for Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IR	Infrared spectroscopy
JP	Japanese pharmacopeia
LAT	Latanoprost ophthalmic solution 0.005% (containing 0.005% latanoprost)
LC-ESI-MS/MS	Liquid chromatography-electrospray ionization-tandem mass spectrometry
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MF	Master file
Mikeluna	Mikeluna Combination Ophthalmic Solution
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
PE	Polyethylene
PG	Prostaglandin
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
SOC	System organ class
$t_{1/2}$	Elimination half-life
t_{max}	Time to maximum concentration

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Carteolol hydrochloride, a β-blocker, and latanoprost, a prostaglandin (PG) $F_{2\alpha}$ derivative, are the active ingredients of the product, Mikeluna combination ophthalmic solution (Mikeluna hereinafter). In Japan, the eye drops containing single active ingredient of either carteolol hydrochloride (1% or 2% carteolol hydrochloride) or latanoprost (0.005% latanoprost) (Mikelan Ophthalmic Solution 1% or 2%, or Xalatan Eye Drop 0.005%, respectively) were approved, indicated for glaucoma and ocular hypertension, in February 1984 and March 1999, respectively. Sustaining formulations of 1% or 2% carteolol hydrochloride alone (Mikelan LA Ophthalmic Solution 1% or 2%) were also approved for the same indications in April 2007. Combination eye drops approved, indicated for glaucoma and ocular hypertension, in Japan include timolol maleate/tafluprost, timolol maleate/travoprost, timolol maleate/dorzolamide hydrochloride, timolol maleate/brinzolamide, and timolol maleate/latanoprost. Unlike the above listed products, Mikeluna containing a β-blocker other than timolol maleate has been developed as a new option for treatment of glaucoma. From the perspective of convenience, Mikeluna uses a sustained action technology similar to that used in Mikelan LA ophthalmic solution 2% (containing 2% carteolol hydrochloride) (CAR) to reduce intraocular pressures for 24 hours with once daily instillation.

The applicant has filed an application for marketing approval after confirming the efficacy and safety of Mikeluna in the treatment of glaucoma and ocular hypertension in clinical studies initiated in [redacted] 20[redacted].

As of October 2015, no combination ophthalmic solutions containing carteolol hydrochloride and latanoprost are approved in foreign countries.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance of carteolol hydrochloride, one of the active ingredients of Mikeluna, is included in the Japanese Pharmacopoeia and is the same as that used in the previously approved products Mikelan LA Ophthalmic Solutions 1% and 2% (Approval No. 21900AMZ00063000 and 21900AMZ00064000). In the present application, the retest period of the drug substance has been proposed to [redacted] years because the results from the long-term stability study submitted demonstrated no significant change in quality.

The quality of the drug substance of latanoprost, the other active ingredient, is described below.

2.1.1 Characterization

The drug substance (latanoprost) is a pale yellow to yellow viscous liquid and its descriptions, solubility, and specific rotation have been determined.

The chemical structure of the drug substance has been confirmed by infrared spectroscopy (IR), ^{1}H-nuclear magnetic resonance (NMR) spectroscopy, ^{13}C-NMR, mass spectrometry (MS), elemental analysis, and optical rotation.

2.1.2 Manufacturing process

The manufacturing process for the drug substance is as registered in master file (MF) (MF registration number [redacted]), which is the same method as that used to manufacture the previously approved products.

2.1.3 Control of drug substance

The proposed specifications and test methods for the drug substance consist of content, description, identification (IR), optical rotation, purity (related substances [high performance liquid chromatography (HPLC)] and residual solvent [gas chromatography (GC)]), water content, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

Table 1 lists stability studies for the drug substance.

Table 1. Stability studies for the drug substance

Study	Standard batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 production batches	5°C	Not controlled	Brown glass vial	60 months
Accelerated	3 production batches	30°C	65% RH		6 months

Based on the above, the retest period for the drug substance has been proposed to [redacted] months when stored refrigerated in a brown glass vial.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an ophthalmic solution containing carteolol hydrochloride 20 mg and latanoprost 50 μg per mL. The drug product contains alginic acid, boric acid, disodium edetate hydrate, polysorbate 80, sodium hydroxide, and purified water as excipients.

2.2.2 Manufacturing process

The drug product is produced through the manufacturing process comprising preparation, [redacted], packaging, and labeling. Preparation and [redacted] have been defined as critical steps, for which process controls have been established.

2.2.3 Control of drug product

The proposed specifications and test methods for the drug product consist of content, description, identification (HPLC), osmotic pressure ratio, pH, related substances (HPLC), foreign insoluble matter, insoluble particle, sterility, [redacted], and assay (carteolol hydrochloride [HPLC] and latanoprost [HPLC]).

2.2.4 Stability of drug product

Table 2 lists stability studies for the drug product. The photostability testing indicated that the drug product was photolabile when placed in a clear glass vial, but was photostable when filled in a titanium oxide containing polyethylene (PE) container.

Table 2. Stability studies for the drug product

Study	Standard batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot batches	25°C	40% RH	Titanium oxide containing PE container (in carton)	18 months
Accelerated	3 pilot batches	40°C	20% RH		6 months

Based on the above, the storage period of the drug product has been proposed to be 30 months when stored at room temperature in a titanium oxide containing PE container according to ICH Q1E Guideline. The long-term testing will be continued for 36 months.

2.R Outline of the review conducted by PMDA

PMDA concluded that the qualities of the drug substances and the drug product are appropriately controlled on the basis of the submitted data and the discussions below.

2.R.1 Coloring of drug product

Because the drug product tended to turn pale yellow in stability studies, PMDA asked the applicant to explain the cause, and its relationship to the stability of the drug product.

The applicant's explanation:

Since CAR with [redacted] (formulated similarly to Mikeluna) was also found to turn pale yellow after storage at 60°C for 2 months, the coloring of Mikeluna seems to be derived from [redacted]. In addition, CAR was found to be colored only in the stress testing, while Mikeluna was observed to be colored in both the accelerated and long-term testing. For CAR, since [redacted], the degree of [redacted] was considered to differ from that of Mikeluna. Besides, since the stability study of Mikeluna showed that all other study items met the specifications at the time point at which coloring was observed and the primary stimulation test in rabbit ocular mucosa confirmed the safety of CAR with coloring, the applicant considered that the coloring is not a quality change that affects the safety of Mikeluna.

PMDA accepted the applicant's explanation.

2.R.2 Stability after opening the container

PMDA asked the applicant to explain any quality changes that might result during repeated use after opening the container.

The applicant's explanation:

Assuming repeated use of a bottle of Mikeluna once daily for a month, stability of Mikeluna (filled in a titanium oxide containing PE container) was studied by instilling a drop once daily and storing the container at uncontrolled room temperature and humidity under white fluorescence lighting (illuminance: 800 lx) for 35 days. No marked change was observed in description, osmotic pressure ratio, pH, related substances (HPLC), foreign insoluble matter, [redacted], and content (carteolol hydrochloride [HPLC] and latanoprost [HPLC]). On the basis of the study results, the applicant will provide information that the residual drug solution should not be used approximately 1 month or later after opening the container.

PMDA accepted the applicant's explanation.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The present application is for a new combination drug. The active ingredients, carteolol hydrochloride (2%) and latanoprost (0.005%), are both ingredients in approved drugs and appear to provide additive effects when used in combination (*Ganka Rinsho Kiyo.* 2010; 3: 14-17). Therefore, non-clinical pharmacology data were considered to be assessed already when each drug was approved as a single agent, and no new study results have been submitted in this application.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Absorption and distribution study results in rabbits were submitted in the present application. Concentrations of carteolol and latanoprost free acid (active substance) in rabbit plasma and ocular tissue were measured by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) (lower limit of quantification [LLQ] of carteolol is 10 ng/mL in aqueous humor, 40 ng/g in ocular tissue other than aqueous humor, and 0.5 ng/mL in plasma; LLQ of latanoprost free acid is 1 ng/mL in aqueous humor, 4 ng/g in ocular tissue other than aqueous humor, and 0.05 ng/mL in plasma). Unless otherwise specified, pharmacokinetic [PK] parameters are expressed in mean ± SD. As for metabolism and excretion, no new studies have been performed because carteolol hydrochloride and latanoprost have different metabolic pathways (metabolism via cytochrome P450 2D6 and hydrolysis by tissue esterase, respectively) and the PK of both drugs administered in combination after migration to the body do not appear to be different from PK of each drug administered as single agent.

4.1. Absorption

Table 3 lists the plasma PK parameters of carteolol and latanoprost free acid after single dose of Mikeluna, CAR or Latanoprost ophthalmic solution 0.005% (containing 0.005% latanoprost) (LAT) 25 μL in both eyes of male pigmented rabbits (n = 3/drug). Plasma C_{max} and $AUC_{0-\infty}$ of carteolol were lower after administration of Mikeluna than after administration of CAR. Plasma C_{max} and AUC_{0-last} of latanoprost free acid were lower after administration of Mikeluna than after LAT (CTD 4.2.2.2-1).

Table 3. Plasma PK parameters of carteolol and latanoprost free acid after single dose of Mikeluna, CAR or LAT in both eyes of male pigmented rabbits

	Drug	C_{max} (ng/mL)	t_{max} (h)[a)]	$t_{1/2}$ (h)	AUC (ng•h/mL)[b)]
Plasma carteolol	Mikeluna	27.50 ± 14.06	0.25 (0.25, 0.50)	1.3 ± 0.2	38.71 ± 14.65
	CAR	38.74 ± 15.63	0.25 (0.25, 0.50)	1.7 ± 0.1	55.93 ± 20.27
Plasma latanoprost free acid	Mikeluna	0.2398 ± 0.0180	0.25 (0.25, 0.25)	-	0.0707 ± 0.0060
	LAT	0.4152 ± 0.1565	0.25 (0.25, 0.25)	-	0.1605 ± 0.0772

Mean ± SD, n = 3/drug

a) Median (min, max)

b) Plasma carteolol, $AUC_{0-\infty}$; plasma latanoprost free acid, AUC_{0-last}

4.2 Distribution

Ocular tissue PK parameters of carteolol and latanoprost free acid after single dose of Mikeluna, CAR or LAT 25 μL in both eyes of male pigmented rabbits were as listed in Table 4. C_{max} and AUC_{0-6h} of carteolol in the aqueous humor and the iris and ciliary body after administration of Mikeluna were 1.7 to 2.2 times those after administration of CAR, without marked differences in the cornea or conjunctiva. C_{max} of latanoprost free acid in the conjunctiva was lower after administration of Mikeluna than after LAT, while AUC_{0-6h} was comparable. No marked differences between Mikeluna and LAT were found in the PK parameters in other ocular tissues after their administration (CTD 4.2.2.2-1).

Table 4 Ocular tissue PK parameters of carteolol and latanoprost free acid after single dose of Mikeluna, CAR, or LAT in both eyes of male pigmented rabbits

Ocular tissue carteolol						
Parameter	C_{max}[a)]		t_{max} (h)		AUC_{0-6h}[b)]	
Drug	Mikeluna	CAR	Mikeluna	CAR	Mikeluna	CAR
Aqueous humor	780.8	455.6	1.00	1.00	2139	1107
Iris and ciliary body	7801	3576	2.00	6.00	31,690	16,620
Cornea	6876	5425	1.00	2.00	16,300	14,920
Conjunctiva	2233	1954	1.00	1.00	4372	6755
Ocular tissue latanoprost free acid						
Parameter	C_{max}[a)]		t_{max} (h)		AUC_{0-6h}[b)]	
Drug	Mikeluna	LAT	Mikeluna	LAT	Mikeluna	LAT
Aqueous humor	105.2	88.82	1.00	2.00	284.5	286.6
Iris and ciliary body	104.8	93.67	0.50	0.50	257.0	236.3
Cornea	962.4	885.3	0.50	0.50	2116	1916
Conjunctiva	63.55	137.4	1.00	0.50	113.4	112.0

Calculated from means at respective time points; n = 2-3 /time point

a) Aqueous humor, ng/mL; iris and ciliary body, cornea and conjunctiva, ng/g

b) Aqueous humor, ng·h/mL; iris and ciliary body, cornea and conjunctiva, ng·h/g

4.R Outline of the review by PMDA

4.R.1 Differences in PK between Mikeluna and CAR

PMDA asked the applicant to explain the cause of the trend observed in rabbits wherein carteolol concentrations were lower in plasma and higher in the aqueous humor and the iris and ciliary body after administration of Mikeluna than after CAR, as well as possible similarities in the distribution of Mikeluna between humans and rabbits and the influence on the safety by differences in PK between CAR and Mikeluna.

The applicant's explanation:

Corneal permeability of drugs is generally affected by the physical properties of drugs and the condition of the cornea, as well as pH, viscosity, and vehicle properties of eye drops (*Qualified Ophthalmic Practice for Specialists* Vol. 11: *Medication Guide for Glaucoma* [in Japanese]. Nakayama

Shoten;2012.76-81) and edetate sodium hydrate, one of the excipients of Mikeluna, enhances carteolol corneal permeability in rabbits (*Pharm Res*. 1995;12:1146-1150). Because the rabbit PK study indicated higher carteolol C_{max} in the aqueous humor and the iris and ciliary body after administration of Mikeluna than after administration of CAR (Table 4), the possibility cannot be ruled out that excipients in Mikeluna have changed the migration properties of carteolol into the eyes. However, the incidence of ocular disorder-related adverse events[1] in the Japanese Phase III studies was 15.8% (31 of 196 subjects) in the Mikeluna group[2] and 5.1% (4 of 78 subjects) in the CAR group.[3] Although the incidence was higher in the Mikeluna group, all events were mild. There was no difference in the incidence of adverse events related to the inner segments of the eyes, including the aqueous humor and the iris and ciliary body (e.g., visual impairment and ciliary hyperaemia), where carteolol concentrations were higher after administration of Mikeluna than after CAS. Consequently, although the possibility cannot be ruled out that carteolol is distributed locally in the eyes at higher concentrations after administration of Mikeluna than after carteolol as a single agent, this is unlikely to pose a clinically significant problem.

PMDA accepted the applicant's explanation.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the active ingredients of Mikeluna, carteolol hydrochloride (2%) and latanoprost (0.005%), are both ingredients in approved drugs and their safety has already been assessed, the results of the local tolerance study were submitted instead in this application. This study was to confirm the safety locally in the eyes after administration of Mikeluna consisting of a combination of these ingredients.

5.1 Other studies

5.1.1 Local tolerance

5.1.1.1 Primary ocular irritation study in pigmented rabbits (CTD 4.2.3.6-1)

In male Dutch rabbits (n = 3/group), saline, vehicle,[4] or Mikeluna 50 μL was administered in the right eye 4 times in total, 2 hours apart. The left eye remained untreated as the control. Ophthalmologic study identified no changes attributable to administration of Mikeluna.

5.1.1.2 Two-week cumulative irritation study in pigmented rabbits (CTD 4.2.3.6-2)

In male Dutch rabbits (n = 5/group), saline, vehicle,[4] or Mikeluna 50 μL was administered in the right eye twice daily, 4 hours apart, for 2 weeks. The left eye remained untreated as the control. Ophthalmologic study identified no changes attributable to administration of Mikeluna.

5.R Outline of the review by PMDA

Based on the submitted study results, PMDA concluded that the combination of carteolol hydrochloride and latanoprost posed no new toxicological concerns.

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1 Events categorized into MedDRA system organ class (SOC) "Ocular disorders"
2 Pooled results from Study 1085EL-[redacted]-002 (CTD 5.3.5.1-01) and Study 1085EL-[redacted]-003 (CTD 5.3.5.1-02)
3 Study 1085EL-[redacted]-003 (CTD 5.3.5.1-02)
4 The formulation used had the same formula as Mikeluna except the active ingredient.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The applicant submitted the results from multiple dose study in healthy adult Japanese men (CTD 5.3.3.1-01, Study 1085EL-[redacted]-001; CTD 5.3.3.1-02, Study 1085EL-[redacted]-004). Plasma carteolol and latanoprost free acid concentrations were measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS) (LLQ of carteolol, 0.02 ng/mL; LLQ of latanoprost free acid, 0.01 ng/mL). Unless otherwise specified, PK parameters are expressed in mean or mean ± SD.

6.1 Studies in healthy adults

In healthy adult Japanese men (10 subjects for PK evaluation), 1 drop of Mikeluna was administered once daily (in the morning) in both eyes for 7 days. Plasma carteolol concentrations on Days 1, 4, and 6 all reached, 15 minutes after administration, their peaks of 1.006 ± 0.6022, 1.141 ± 0.4793 and 1.415 ± 0.8524 ng/mL, respectively. Plasma latanoprost free acid concentrations on Days 1, 4, and 6 all reached, 5 minutes after administration, their peaks of 17.61 ± 12.42, 23.83 ± 17.53, 29.57 ± 22.81 pg/mL, all of which fell below the LLQ 1 hour after administration in all subjects (CTD 5.3.3.1-01, Study 1085EL-[redacted]-001).

In healthy adult Japanese men (30 subjects for PK evaluation), 1 drop of Mikeluna, CAR, or LAT was administered once daily (in the morning) in both eyes for 7 days. Table 5 lists the PK parameters of plasma carteolol and latanoprost free acid. While C_{max} and $AUC_{0\text{-}24h}$ of plasma carteolol on Day 7 were slightly lower for Mikeluna than for CAR, plasma latanoprost free acid concentrations showed no marked differences between Mikeluna and LAT. A comparison of PK parameters of plasma carteolol and latanoprost free acid between Day 1 and Day 7 showed the C_{max} of plasma carteolol was higher on Day 7 than on Day 1 for both Mikeluna and CAR, while none of the PK parameters of plasma latanoprost free acid showed marked differences between Day 1 and Day 7 for either Mikeluna or LAT (CTD 5.3.3.1-02, Study 1085EL-[redacted]-004).

Table 5. PK parameters of plasma carteolol and latanoprost free acid when Mikeluna, CAR, or LAT was administered once daily for 7 days in healthy adult Japanese men (Study 1085EL-[redacted]-004)

Plasma carteolol					
Drug		C_{max} (ng/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)[b]
Mikeluna	Day 1	0.8558 ± 0.2658	0.25 (0.25, 4.00)	13.9 ± 7.32[c]	11.0 ± 7.48[d]
	Day 7	1.174 ± 0.3085	0.25 (0.25, 4.00)	13.5 ± 2.34	11.6 ± 2.97
CAR	Day 1	0.9984 ± 0.4832	0.25 (0.25, 23.92)	12.5 ± 2.92[c]	12.7 ± 4.17[c]
	Day 7	1.627 ± 0.5001	0.38 (0.25, 24.00)	14.1 ± 2.77[c]	18.0 ± 5.90
Plasma latanoprost free acid					
Drug		C_{max} (pg/mL)	t_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0\text{-}0.5h}$ (pg·h/mL)
Mikeluna	Day 1	19.77 ± 10.13	0.17 (0.083, 0.17)[d]	0.30 ± 0.058[e]	6.15 ± 2.42[d]
	Day 7	18.47 ± 8.913	0.083 (0.083, 0.17)[d]	0.19, 0.21[f]	4.97 ± 1.96[d]
LAT	Day 1	21.22 ± 10.16	0.17 (0.083, 0.17)[d]	0.25 ± 0.062[g]	6.68 ± 3.08[d]
	Day 7	17.48 ± 8.892	0.17 (0.083, 0.17)[d]	0.28, 0.35[f]	5.31 ± 2.72[d]

Mean ± SD, n = 10/drug
a) Median (minimum, maximum)
b) $AUC_{0\text{-}\infty}$ for single administration
c) 6 subjects, d) 9 subjects, e) 4 subjects, f) individual values of 2 subjects, g) 5 subjects

6.R Outline of the review by PMDA

PMDA concluded that the combination of carteolol hydrochloride and latanoprost posed no new problems from the PK perspective, based on the study results submitted.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

As efficacy and safety data, results from 2 Japanese Phase III studies in Japanese subjects (CTD 5.3.5.1-01, Study 1085EL-[redacted]-002; CTD 5.3.5.1-02, Study 1085EL-[redacted]-003) were submitted. Results from 2 Japanese Phase I studies in healthy adult Japanese men (CTD 5.3.3.1-01, Study 1085EL-[redacted]-001; CTD 5.3.3.1-02, Study 1085EL-[redacted]-004) were submitted as safety evaluation data. Furthermore, results from specified drug use-results survey for CAR were submitted as reference data (CTD 5.3.6-01 and CTD 5.3.6-03). Treatment groups without specific description of adverse events indicate that no events were reported in them.

7.1 Phase I studies

7.1.1 Japanese Phase I study (CTD 5.3.3.1-01, Study 1085EL-[redacted]-001 [[redacted] to [redacted] 20[redacted]])

In healthy adult Japanese men (target sample size, 15 in total; 5 in the placebo group and 10 in the Mikeluna group), a randomized, subject-blinded, placebo-controlled, parallel group study was performed to evaluate safety and efficacy of Mikeluna when administered in multiple doses [For PK, see "6.1 Studies in healthy adult men"].

Subjects received 1 drop of placebo or Mikeluna once daily (in the morning) in both eyes for 7 days.

All 15 randomized subjects (5 in the placebo group and 10 in the Mikeluna group) were included in the safety analysis population, and no subjects discontinued the study.

Adverse events (including laboratory test abnormal)[5] were found in 100% (10 of 10) of subjects in the Mikeluna group. No deaths, other serious adverse events, or adverse events led to study discontinuation.

Adverse events (including laboratory test abnormal) for which a causal relationship to the study drug was not ruled out were found in 90% (9 of 10) of subjects in the Mikeluna group, and a major event was conjunctival hyperaemia (9 subjects).

There were no clinically significant changes in or observations of vital signs (blood pressure, pulse rate, and body temperature), ECG, and ophthalmologic tests (visual acuity, external region, pupil diameter, and ocular fundus).

7.1.2 Japanese Phase I study (CTD 5.3.3.1-02, Study 1085EL-[redacted]-004 [April to May 2014])

A randomized, open-label, CAR- and LAT-controlled, parallel group study was conducted to assess the safety and PK of Mikeluna when administered in multiple doses in healthy adult Japanese men (target sample size, 30 in total; 10/group) [for PK, see "6.1 Studies in healthy adult men"].

Subjects received 1 drop of Mikeluna, CAR or LAT once daily (in the morning) in both eyes for 7 days.

All 30 randomized subjects (10 each in the Mikeluna, CAR and LAT groups) were included in the safety analysis population, and no subjects discontinued the study.

Adverse events (including laboratory test abnormal)[6] were found in 60% (6 of 10) of subjects in the Mikeluna group, 40% (4 of 10) of subjects in the CAR group, and 80% (8 of 10) of subjects in the LAT group. No deaths, serious adverse events, or adverse events led to study discontinuation.

[5] MedDRA/J ver. 16.0
[6] MedDRA/J ver. 17.0

Adverse events for which a causal relationship to the study drug was not ruled out (including laboratory test abnormal) were found in 60% (6 of 10) of subjects in the Mikeluna group, 40% (4 of 10) of subjects in the CAR group, and 80% (8 of 10) of subjects in the LAT group. Major events included conjunctival hyperaemia (6 subjects in the Mikeluna group, 3 in the CAR group, and 8 in the LAT group) and corneal disorder (3 in the LAT group).
There were no clinically significant changes in or observations of vital signs (blood pressure, pulse rate and body temperature), ECG, or ophthalmologic tests (visual acuity and ocular fundus).

Consequently, the applicant explained that no major safety problems were found in multiple dose administration of Mikeluna in healthy adult Japanese men.

7.2 Phase III studies

7.2.1 Japanese Phase III study (CTD 5.3.5.1-01, Study 1085EL-[redacted]-002 [April 2014 to March 2015])

A randomized, evaluator-blinded,[7] LAT-controlled, parallel-group study was conducted to evaluate the efficacy and safety of Mikeluna in Japanese patients who had been diagnosed with primary open angle glaucoma or ocular hypertension and had unilateral intraocular pressure ≥18 mmHg and bilateral ocular pressure <35 mmHg at baseline, after the end of the 4-week run-in treatment with LAT and before study treatment (target sample size, 220 in total; 110/group).
Patients received 1 drop of LAT once daily (in the morning) in both eyes for 4 weeks in the run-in period, and then 1 drop of Mikeluna or LAT once daily (morning) in both eyes for 8 weeks.
Of 238 randomized patients (119 in the Mikeluna group and 119 in the LAT group), 237 (118 in the Mikeluna group and 119 in the LAT group) were included in full analysis set (FAS), that is, the safety analysis population and efficacy analysis population. Excluded was 1 patient who did not receive study drug in the Mikeluna group. Study treatment was discontinued in 8 patients (5 in the Mikeluna group and 3 in the LAT group). The major reasons included occurrence of adverse events (in 1 and 2[8] patients in the respective groups), use of prohibited concomitant medications (in 2 patients in the Mikeluna group), and patient's will (in 2 in the Mikeluna group).
The reduction of intraocular pressure from baseline until study drug administration in the morning at Week 8 in FAS, the primary endpoint, are shown in Table 6, indicating statistically significant difference between the Mikeluna group and LAT group ($P < 0.0001$, analysis of covariance (ANCOVA) with treatment groups as factors and baseline value as covariate).

[7] Because the same container could not be used for both Mikeluna and LAT from the view of quality assurance, the study was performed as a single-blind study (evaluator-blinded). However, the study was also designed to ensure blindness to the patients as much as possible by packaging each drug bottle in a small carton indistinguishable from each other for a consistent appearance.
[8] In the 2 patients from the LAT group, discontinuation was due to adverse events that had developed before initiation of administration of the study drug.

Table 6. Reduction in intraocular pressure from baseline until study drug administration in the morning at Week 8 (Study 1085EL-[redacted]-002, FAS, Last observation carried forward [LOCF])

Treatment group	Number of patients[a)]	Intraocular pressure (before morning administration)		Reduction of intraocular pressure[b)]	Between-group comparison[c)]	
		Baseline	Week 8		Difference[d)]	*P*-value
Mikeluna	117	20.1 ± 2.2	17.2 ± 2.7	2.9 ± 2.0	1.3 [0.7, 1.8]	$P < 0.0001$
LAT	118	20.0 ± 1.9	18.4 ± 2.7	1.6 ± 2.3		

Mean ± SD (mmHg)

a) Of patients in FAS, patients who had intraocular pressure measured at baseline and before administration at ≥1 time point durint the study were included in the analysis.
b) Intraocular pressure at baseline – intraocular pressure at Week 8
c) Based on an ANCOVA model with treatment group as the factor and baseline value as the covariate
d) Mikeluna – LAT [95% confidence interval (CI)]

Adverse events (including laboratory test abnormal)[6] were found in 25.4% (30 of 118) of patients in the Mikeluna group and 19.3% (23 of 119) of patients in the LAT group. No deaths or other serious adverse events were reported. Adverse events leading to study discontinuation were experienced by 1 patient in the Mikeluna group (visual impairment and eye pruritus), for which a causal relationship to the study drug was not ruled out.

Adverse events for which a causal relationship to the study drug was not ruled out (including laboratory test abnormal) were found in 6.8% (8 of 118) of patients in in the Mikeluna group and 4.2% (5 of 119) patients in in the LAT group. Major events included growth of eyelashes (in 2 and 1 patients in the respective groups), vision blurred (in 2 in the Mikeluna group), eye pruritus (in 1 and 1 patients in the respective groups), and blepharal pigmentation (in 2 in the LAT group).

As for vital signs (blood pressure and pulse rate), hypertension was found in 1 patient in the LAT group; a causal relationship to the study drug was ruled out.

On the basis of the findings above, the applicant explained that the superiority of Mikeluna over LAT has been demonstrated for efficacy without major safety problems in Japanese patients with primary open angle glaucoma and ocular hypertension.

7.2.2 Japanese Phase III study (CTD 5.3.5.1-02, Study 1085EL-[redacted]-003 [April 2014 to January 2015])

A randomized, double-blind,[9] CAR-controlled, parallel-group study was conducted to evaluate the efficacy and safety of Mikeluna in Japanese patients who had been diagnosed with primary open angle glaucoma or ocular hypertension and exhibited unilateral ocular pressure ≥18 mmHg and bilateral ocular pressure <35 mmHg at baseline, after the end of the 4-week run-in treatment with CAR (baseline) and before study treatment (target sample size, 175 in total; 70 in the Mikeluna group, 70 in the CAR group, and 35 in the CAR+LAT group).

Patients received 1 drop of CAR once daily (in the morning) in both eyes for 4 weeks in the run-in phase, followed by 1 drop of Mikeluna or CAR once daily (in the morning) in both eyes for 8 weeks. In the CAR+LAT group, patients received 1 drop of LAT and CAR each once daily (in the morning)[10] in both eyes for 8 weeks following the run-in period.

All 193 randomized patients (78 in the Mikeluna group, 78 in the CAR group, and 37 in the CAR+LAT group) were included in FAS, that is, the safety analysis population and efficacy analysis population.

[9] In the CAR＋LAT group, the study was performed as a single-blind study (evaluator-blind) because the number of bottles differed from the Mikeluna group and CAR group.
[10] In the CAR+LAT group, by study protocol, LAT was administered first, and then CAR was 10 minutes later.

Study treatment was discontinued in 4 patients (2, 2, and 0, respectively). The major cause was adverse events (2, 1, and 0, respectively).

Results in the primary endpoint, reductions of intraocular pressure from baseline before administration in the morning at Week 8 of study drug administration in FAS, were as indicated in Table 7, with statistically significant difference between the Mikeluna group and CAR group ($P < 0.0001$, ANCOVA with treatment groups as factors and baseline value as covariate). Reductions of intraocular pressure were similar between the Mikeluna group and the CAR+LAT group.

Table 7. Reductions of intraocular pressure from baseline before administration in the morning at Week 8 of study drug administration (Study 1085EL-[redacted]-003, FAS, LOCF)

Treatment group	Number of patients[a)]	Intraocular pressure (before morning administration)		Reductions of intraocular pressure[b)]	Intergroup comparison[c)]	
		Baseline	Week 8		Difference[d)]	*P*-value
Mikeluna	78	19.8 ± 1.7	16.3 ± 2.1	3.5 ± 1.9	1.9 [1.3, 2.5]	$P < 0.0001$
CAR	77	19.9 ± 2.4	18.2 ± 2.7	1.6 ± 1.9		
CAR+LAT	37	19.7 ± 2.1	16.6 ± 2.6	3.1 ± 2.3		

Mean ± SD (mmHg)

a) Of patients in FAS, patients who had intraocular pressure measured at baseline and before administration at ≥1 time point during the study were included in the analysis.
b) Intraocular pressure at baseline – intraocular pressure at Week 8
c) Based on an ANCOVA model with treatment group as the factor and baseline value as the covariate
d) Mikeluna – CAR [95% CI]

Adverse events (including laboratory test abnormal)[6] were found in 32.1% (25 of 78) of patients in the Mikeluna group, 15.4% (12 of 78) of patients in the CAR group, and 21.6% (8 of 37) of patients in the CAR+LAT group. No deaths were reported, and subdural haematoma, a serious adverse event, was found in 1 patient in the CAR group, but a causal relationship to the study drug was ruled out. Adverse events leading to study discontinuation were found in 1 patient in the Mikeluna group (eye pain) and 1patient in the CAR group (subdural haematoma). A causal relationship to the study drug was not ruled out for eye pain.

Adverse events for which a causal relationship to the study drug was not ruled out (including laboratory test abnormal) were found in 19.2% (15 of 78) of patients in the Mikeluna group, 2.6% (2 of 78) of patients in the CAR group, and 16.2% (6 of 37) of patients in the CAR+LAT group. The major events included eye pain (in 3, 0, and 0 patients in the respective groups), conjunctival hyperaemia (in 2, 1, and 2 patients, respectively), eye irritation (in 2, 0, and 1patients, respectively), ocular hyperaemia (in 2, 0, and 1patients, respectively), abnormal sensation in eye, blepharitis, abnormal sensation in eye, and eye pruritus (each in 2, 0, and 0 patients, respectively), and corneal disorder (in 1, 0, and 1 patients, respectively).

As for vital signs (blood pressure and pulse rate), hypertension was experienced by 1 patient in the Mikeluna group. A causal relationship to the study drug was excluded.

On the basis of the findings above, the applicant explained that the superiority of Mikeluna over CAR has been demonstrated for efficacy without major safety problems in Japanese patients with primary open angle glaucoma and ocular hypertension.

7.R Outline of the review by PMDA

7.R.1 Rationale for the combination in Mikeluna and its clinical positioning

PMDA asked the applicant to explain the rationale for the combination in Mikeluna on the basis of actual medications prescribed for glaucoma and ocular hypertension in Japan.

The applicant's explanation:

In medications for glaucoma and ocular hypertension, multiple drugs are administered if a single medication cannot achieve sufficient reductions in intraocular pressure. However, the volume the conjunctival sac can retain at one time is close to 1 drop of ocular solution, which poses a concern that drug effects may be weakened in sequential instillations of more than 1 drug because the drug administered earlier is washed away with the next one. Therefore, an interval of ≥5 minutes is generally necessary between administration. In addition, multiple medications pose the problem of poor adherence in patients (*Ophthalmic Surg*. 1995;26:233-236; *Ophthalmology*. 2005;112:863-868). The Japan Glaucoma Society Guidelines for Glaucoma ed. 3 (*Nippon Ganka Gakkai Zasshi*. 2012;116:3-46) states that combination eye drops should also be considered to improve adherence in multiple drug therapy. Besides, the use-results survey performed in 2012 indicated that patients with glaucoma or ocular hypertension on double, triple, quadruple, and quintuple therapy accounted for 22.9%, 9.1%, 2.9%, and 0.4% of total patients, respectively (*Atarashii Ganka*. 2013;30:851-856). IMS MDI data (20[redacted]) based on the numbers of drug prescriptions also indicated use of concomitant eye drop(s) in about 43% of all prescriptions for Mikelan LA ocular solution or Mikelan ocular solution, both of which include carteolol hydrochloride as an active ingredient. On the basis of the finding above, the applicant considers that use of a combination drug reduces the number of coadministered drugs and is expected to improve convenience and adherence in patients with glaucoma and ocular hypertension on more than one drug.

PMDA asked the applicant to explain the clinical positioning of Mikeluna, a combination drug.

The applicant's explanation:

In Japan, combination eye drops approved as drugs for glaucoma all contain a β-blocker timolol maleate. Carteolol hydrochloride is known to have lesser effects on the cardiovascular system (*Adv Ther*. 1993; 10:95-131), respiratory function (*Gendai Iryo*. 1984; 16:1259-1263), eye irritation (*Am J Ophthalmol*. 1988; 105:150-154), and blood lipids (*J Glaucoma*. 1996;5:252-257) than timolol maleate. Latanoprost is the most commonly used drug for glaucoma treatment, and IMS MDI data (20[redacted]) based on the numbers of drug prescriptions indicate that latanoprost is coadministered most often with Mikelan LA ocular solution and Mikelan ocular solution among PG drugs. Besides, Mikeluna is a combination drug of a PG drug and a β-blocker, the most common combination, and may be a new option as a combination drug containing a β-blocker other than timolol maleate. While the Japan Glaucoma Society Guidelines for Glaucoma.ed. 3 states that the primary purpose of combination eye drops is to improve adherence to multiple therapies and they are not first-line drugs, combination eye drops may be used as first-line drugs in patients with markedly high ocular tension for whom the target ocular tension is unlikely to be achieved with a single agent or patients with severe visual field defect requiring immediate decrease in

intraocular pressure (*Qualified Ophthalmic Practice for Specialists*. Vol. 11: *Medication Guide for Glaucoma* [in Japanese]. Nakayama Shoten; 2012:192-196). Besides, although combination eye drops including Mikeluna may be used as first-line drugs for glaucoma, the applicant will state that treatment with single agent eye drops should be tried first in principle, as in the previously approved combination eye drops, in the Precautions for Indications of the package insert for Mikeluna.

PMDA's view:
Since multiple therapies raise concerns that the drug instilled earlier may be washed away by the next drug in an inappropriate instillation interval and therefore an instillation interval of ≥5 minutes is necessary, Mikeluna seems to improve convenience for patients. In addition, although glaucoma drugs containing a combination of a β-blocker timolol maleate and a PG drug have already been approved, Mikeluna may be an option in the treatment of glaucoma, since it contains a β-blocker other than timolol maleate. Besides, as indicated in the Japan Glaucoma Society Guidelines for Glaucoma. ed. 3, medication for glaucoma should basically be single agent therapy, and therefore, the Precautions for Indications of the package insert of Mikeluna should also include a statement that treatment with single eye drops should be tried first in principle, as in the previously approved combination eye drops.

7.R.2 Efficacy

7.R.2.1 Efficacy based on diurnal variation of intraocular pressure

PMDA asked the applicant to explain sustained effects of Mikeluna on the reduction of intraocular pressure throughout the day.

The applicant's explanation:
First, the approved carteolol hydrochloride eye drops have 2 variations in terms of ingredient concentrations, that is, 1% concentration product and 2% concentration product, and it is specified that the 2% product is to be used if the 1% product has inadequate effect (Mikelan LA ophthalmic solution [package insert]). Because the target patient population of combination eye drops is those who cannot achieve sufficient reductions in intraocular pressure with single-agent therapy, carteolol hydrochloride 2% was selected for Mikeluna. Also latanoprost 0.005%, the same concentration as in the approved latanoprost products, was selected. Second, the effect of latanoprost on the reduction of intraocular pressure peaks about 8 to 12 hours after administration (*Kiso-to-Rinsho*. 1995;29:4271-4285; *Am J Ophthalmol*. 1999;128:15-20) and β-blockers 2 hours after the administration (*Glaucoma*. [in Japanese]. Igaku-Shoin; 2004:333-335). In Japanese Phase III studies, therefore, intraocular pressure was measured before administration in the morning and at 2 and 8 hours after administration, as it was considered appropriate to measure trough intraocular pressure reduction (at 0 hours) and intraocular pressure reductions when each ingredient exerts its effect most, to evaluate the effects of Mikeluna on intraocular pressure reductions throughout the day. Finally, figure 1 shows time course of intraocular pressure in the Japanese Phase III studies. The differences in intraocular pressure reductions from baseline between the Mikeluna and LAT groups (Mikeluna − LAT) before (at 0 hours) and at 2 and 8 hours after administration at Week 8 with their 95% CI were 1.3 [0.7, 1.8] mmHg, 1.0 [0.5, 1.6] mmHg, and 0.7

[0.2, 1.3] mmHg, respectively, and the differences in intraocular pressure reductions from baseline between the Mikeluna and CAR groups (Mikeluna − CAR) with their 95% CI were 1.9 [1.3, 2.5] mmHg, 2.1 [1.6, 2.7] mmHg, and 2.7 [1.9, 3.5] mmHg, respectively.

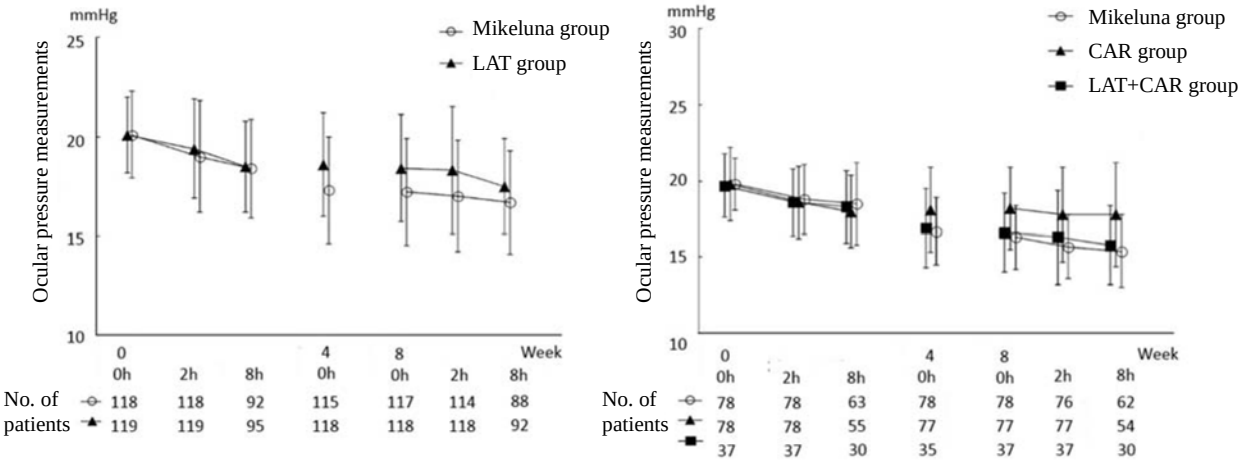

Figure 1. Time course of intraocular pressure (mean ± SD, LOCF)
(Study 1085EL-[redacted]-002 [left], Study 1085EL-[redacted]-003 [right])

In addition, the CAR+LAT group was included in the Japanese Phase III study (Study 1085EL-[redacted]-003) to assess similarities in intraocular pressure reductions between treatment with Mikeluna and treatment with CAR and LAT in combination. The differences in intraocular pressure reductions from baseline between the Mikeluna group and CAR+LAT group (Mikeluna − CAR+LAT) at 0, 2, and 8 hours after administration at Week 8 with their 95% CI were 0.4 [-0.4, 1.1] mmHg, 0.6 [-0.1, 1.4] mmHg and 0.5 [-0.3, 1.4] mmHg. At any time points, Mikeluna tended to decrease intraocular pressure to an equal or greater extent to which CAR+LAT did.

Consequently, the applicant considered that the intraocular pressure reduction achieved with Mikeluna seems to be maintained throughout the day and is not inferior to that with CAR and LAT in combination.

7.R.2.2 Reducing effect on intraocular pressure in long-term treatment

PMDA asked the applicant to explain reducing effect on intraocular pressure in long-term treatment.

The applicant's explanation:

In the specified drug use-results survey of CAR, intraocular pressure values and time course of reduction in intraocular pressure in patients on LAT monotherapy who received CAR concomitantly were as shown in Table 8. On the basis of reductions in intraocular pressure maintained over 12 months and no marked differences in reducing effect on intraocular pressure between 8-week Mikeluna and CAR+LAT treatment [see "7.R.2.1 Efficacy based on diurnal variation of intraocular pressure"], the applicant considered that reduction in intraocular pressure is maintained in long-term treatment with Mikeluna.

Table 8. Time course of intraocular pressure values in patients on LAT monotherapy who received CAR concomitantly (Specified drug use-results survey of CAR)

Treatment duration	Before treatment	4 weeks	8 weeks	3 months	6 months	9 months	12 months
Intraocular pressure values	16.33 ± 5.46 (82)	12.94 ± 3.90 (34)	15.16 ± 6.98 (36)	14.74 ± 4.87 (63)	13.87 ± 4.25 (57)	13.65 ± 3.80 (63)	13.48 ± 4.01 (55)
Reduction in intraocular pressure		1.79 ± 3.26 (34)	0.68 ± 3.11 (35)	1.90 ± 3.93 (61)	1.24 ± 3.05 (55)	1.88 ± 4.14 (61)	1.84 ± 3.15 (55)

Mean ± SD (mmHg) (number of eyes assessed)

PMDA's view:

Since Japanese Phase III studies (Studies 1085EL-[redacted]-002 and 1085EL-[redacted]-003) demonstrated that reduction in intraocular pressure in the Mikeluna group exceeded those in the CAT and LAT monotherapy groups at all time points and showed no marked differences in reduction in intraocular pressure between the CAR+LAT group and the Mikeluna group, the applicant's explanation that reduction in intraocular pressure due to Mikeluna is maintained throughout the day is reasonable. Additionally, on the basis of the specified drug use-results survey of CAR, Mikeluna is also expected to be effective in long-term treatment.

7.R.3 Safety

7.R.3.1 Safety as compared with CAR and LAT monotherapies and their combination therapy

PMDA asked the applicant to explain the safety of Mikeluna as compared with CAR and LAT monotherapies and their combination therapy (CAR+LAT).

The applicant's explanation:

Table 9 shows the incidence of major adverse events observed in the Japanese Phase III studies (Studies 1085EL-[redacted]-002 and 1085EL-[redacted]-003).[6] Although the Mikeluna group tended to show higher incidence of adverse events than the CAR or LAT group, the Mikeluna group tended to exhibit no markedly higher incidence than the CAR+LAT group. All events observed in the Mikeluna group were mild or moderate in severity. No adverse events characteristic of PG drugs[11] tended to occur at higher incidence in the Mikeluna group than in the LAT group or CAR+LAT group. Additionally, although punctate keratitis, blepharitis, eye pain, vision blurred, foreign body sensation in eyes, abnormal sensation in eye, and glucose urine present were observed only in the Mikeluna group, all these events were also found in clinical trials or post-marketing safety information of CAR or LAT. A causal relationship to Mikeluna was not excluded for adverse events leading to study discontinuation in the Mikeluna group (eye pruritus, visual impairment, and eye pain), but they were all mild in severity and resolved after discontinuation of Mikeluna without treatment.

[11] Events categorized into MedDRA preferred term (PT); ciliary hyperaemia, conjunctival hyperaemia, blepharal pigmentation, growth of eyelashes, ocular hyperaemia, iris hyperpigmentation, eyelash thickening, eyelash discoloration, trichomegaly, eyelash hyperpigmentation, hypertrichosis (except that occurring at sites other than the eye), hypertrichosis at the administration site (except that occurring at sites other than the eye), hypertrichosis at the application site (except that occurring at sites other than the eye), instillation site discolouration (except that occurring at sites other than the eye), or administration site discolouration (except that occurring at sites other than the eye).

Table 9. Incidence of major adverse events in the Japanese Phase III Studies (safety analysis population)

Treatment group	Mikeluna[a)]	LAT[b)]	CAR[c)]	CAR＋LAT[c)]
Number of patients analyzed	196	119	78	37
Total adverse events	55 (28.1)	23 (19.3)	12 (15.4)	8 (21.6)
Adverse events leading to study discontinuation	2 (1.0)	0	1 (1.3)	0
Serious adverse events	0	0	1 (1.3)	0
Adverse events related to ocular disorder	33 (16.8)	11 (9.2)	4 (5.1)	8 (21.6)
Adverse events specific to PG drugs	7 (3.6)	4 (3.4)	1 (1.3)	3 (8.1)
Major adverse events				
Nasopharyngitis	6 (3.1)	7 (5.9)	2 (2.6)	0
Punctate keratitis	4 (2.0)	0	0	0
Eye itching	3 (1.5)	2 (1.7)	0	0
Conjunctival hemorrhage	3 (1.5)	0	1 (1.3)	0
Blepharitis	3 (1.5)	0	0	0
Eye pain	3 (1.5)	0	0	0
Blurred vision	3 (1.5)	0	0	0
Foreign body sensation in the eye	3 (1.5)	0	0	0
Conjunctival injection	2 (1.0)	2 (1.7)	1 (1.3)	2 (5.4)
Ocular irritation	2 (1.0)	2 (1.7)	0	1 (2.7)
Eyelash growth	2 (1.0)	1 (0.8)	0	0
Ocular injection	2 (1.0)	0	0	1 (2.7)
Strange feeling in the eye	2 (1.0)	0	0	0
Eyelid pigmentation	0	2 (1.7)	0	0
Positive urine glucose	3 (1.5)	0	0	0

Number of patients with onset (Incidence [%])
a) Pooled results from Studies 1085EL-[redacted]-002 and 1085EL-[redacted]-003
b) Study 1085EL-[redacted]-002
c) Study 1085EL-[redacted]-003

Consequently, the applicant considered that Mikeluna poses no clinically significant safety problems compared to CAR or LAT monotherapy, or their combination therapy CAR+LAT.

7.R.3.2 Safety in long-term treatment and in combination with other glaucoma drugs

Since Mikeluna is assumed to be used for long periods or coadministered with other glaucoma drugs [see "7.R.1 Rationale for the combination in Mikeluna and its clinical positioning"], PMDA asked the applicant to discuss the safety of Mikeluna in long-term treatment and in combination with other glaucoma drugs.

The applicant's explanation:

Although no long-term study of Mikeluna has been performed, specified drug use-results survey of CAR examined safety in long-term treatment (in a 1-year observation period). Table 10 shows the incidence of adverse events[12] observed in patients receiving CAR and LAT concomitantly in the survey.

[12] MedDRA/J ver. 15.1

Table 10. Incidence of adverse events in patients receiving CAR and LAT concomitantly (Specified drug use-results survey of CAR)

	Patients on CAR and LAT		
	Total	In combination with other glaucoma drugs	
		No	Yes
Number of patients analyzed	112	56	56
Total adverse events	12 (10.71)	6 (10.71)	6 (10.71)
Adverse events leading to study discontinuation	3 (2.68)	2 (3.57)	1 (1.79)
Serious adverse events	1 (0.89)	1 (1.79)	0
Adverse events related to ocular disorder	9 (8.04)	4 (7.14)	5 (8.93)
Adverse events specific to PG drugs	1 (0.89)	1 (1.79)	0
All adverse events observed in patients receiving CAR and LAT concomitantly			
Keratitis	2 (1.79)	0	2 (3.57)
Corneal disorder	2 (1.79)	1 (1.79)	1 (1.79)
Conjunctivitis	2 (1.79)	0	2 (3.57)
Blepharitis	1 (0.89)	0	1 (1.79)
Conjunctival hemorrhage	1 (0.89)	0	1 (1.79)
Arrhythmia	1 (0.89)	0	1 (1.79)
Ocular injection	1 (0.89)	1 (1.79)	0
Foreign matter in the eyes	1 (0.89)	1 (1.79)	0
Hemorrhage of vaginae nervi optici	1 (0.89)	1 (1.79)	0
Headache	1 (0.89)	1 (1.79)	0
Laceration	1 (0.89)	1 (1.79)	0
Pneumonia	1 (0.89)	1 (1.79)	0

Number of patients with onset (Incidence [%])

As Table 11 presents the incidence of adverse events by time to onset, events observed after Week 4 of treatment were keratitis and corneal disorder (each in 2 patients), and foreign body in eye, ocular hyperaemia, optic nerve sheath haemorrhage, conjunctival haemorrhage, headache, and laceration (1 patient for each event), and no particular events tended to occur at higher incidence in long-term treatment. The only serious adverse event was pneumonia, which was treated and resolved while the patient was on Mikeluna treatment, and a causal relationship to Mikeluna was excluded. The adverse events leading to study discontinuation (ocular hyperaemia, headache, and arrhythmia in 1 patient each) were all non-serious and resolved or remitted after discontinuation of Mikeluna. Furthermore, patients receiving other glaucoma drugs[13] in addition to CAR and LAT did not tend to experience adverse events at higher incidence than patients receiving only CAR and LAT in combination.

Consequently, the applicant considered it unlikely that any major safety problems arise in long-term treatment with Mikeluna alone or in combination with other glaucoma drugs.

[13] PG drugs, β-blocker, carbonic anhydrase inhibitor, sympathomimetic agents, parasympathomimetic agents, and α_2-blockers

Table 11. Incidence of adverse events in patients receiving CAR and LAT concomitantly by time to onset[a)] (Specified drug use-results survey of CAR)

Number of weeks after initial administration	<4 weeks	≥4 weeks and <12 weeks	≥12 weeks and <24 weeks	≥24 weeks and <36 weeks	≥36 weeks and <48 weeks	≥48 weeks
Number of patients analyzed	112	111	104	96	93	83
Total adverse events	3 (2.68)	4 (3.60)	1 (0.96)	2 (2.08)	2 (2.15)	0
Keratitis	0	0	0	1 (1.04)	1 (1.08)	0
Corneal disorder	0	1 (0.90)	1 (0.96)	0	0	0
Conjunctivitis	2 (1.79)	0	0	0	0	0
Blepharitis	1 (0.89)	0	0	0	0	0
Conjunctival hemorrhage	0	0	0	1 (1.04)	0	0
Ocular injection	0	1 (0.90)	0	0	0	0
Foreign matter in the eyes	0	1 (0.90)	0	0	0	0
Hemorrhage of vaginae nervi optici	0	1 (0.90)	0	0	0	0
Headache	0	0	0	1 (1.04)	0	0
Laceration	0	0	0	0	1 (1.08)	0
Pneumonia	1 (0.89)	0	0	0	0	0

Number of patients with onset (Incidence [%])
a) Time to onset of arrhythmia (1 patient) was unknown.

PMDA's view:

Based on the results from submitted clinical trials, PMDA considers it unlikely that any new safety problems will arise with treatment with Mikeluna compared to CAR or LAT monotherapy or their combination therapy CAR+LAT. However, in the Japanese Phase III studies, adverse events related to ocular disorders, albeit mild, were found only in the Mikeluna group. Additionally, no long-term study of Mikeluna has been performed. Thus, PMDA considers it necessary to examine the safety in long-term treatment in subsequent post-marketing surveillance. Furthermore, although combination therapy with any other glaucoma drugs is unlikely to pose clinically significant safety problems at this time, this issue should continue to be examined in subsequent post-marketing surveillance, since only limited number of relevant cases are available in the specified drug use-results survey of CAR.

7.R.4 Post-marketing investigations

PMDA's view:

Based on the submitted clinical study data and post-marketing safety information on carteolol hydrochloride, PMDA considers that the safety in long-term treatment and in combination with other glaucoma drugs need to be examined continuously in the post-marketing surveillance of Mikeluna.

The applicant's explanation:

As post-marketing surveillance of Mikeluna, the applicant will perform specified drug use-results survey in patients with glaucoma and ocular hypertension with 1-year observation period (planned sample size, 300 patients).

PMDA considers that the appropriateness of these measures will finally be determined after discussion in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-01 and CTD 5.3.5.1-02) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of Mikeluna in the treatment of glaucoma and ocular hypertension and acceptable safety in view of the benefits indicated by the data submitted. Since Mikeluna contains a β-blocker that differs from that contained in the previously approved combination eye drops, it appears to present a new treatment option in the treatment of glaucoma and ocular hypertension. The appropriateness of the post-marketing investigations should be further discussed in the Expert Discussion.

PMDA has concluded that Mikeluna may be approved if Mikeluna is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 15, 2016

Product Submitted for Approval

Brand Name	Mikeluna Combination Ophthalmic Solution
Non-proprietary Name	Carteolol Hydrochloride/Latanoprost
Applicant	Otsuka Pharmaceutical Co., Ltd.
Date of Application	October 1, 2015

1. Content of the Review

Comments made during the Expert Discussion and subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on "7.R.1 Rationale for the combination in Mikeluna and its clinical positioning," "7.R.2 Efficacy," and "7.R.3 Safety" that described in Review Report (1).

PMDA also discussed the following points and took action as necessary.

1.1 Risk management plan (draft)

With regard to the long-term safety of Mikeluna, PMDA asked the applicant to reconsider the period and number of patients of specified drug use-results survey. This is because iris pigmentation, an event characteristic of prostaglandin drugs, may develop in association with administration of Mikeluna for a certain period, based on the review presented in "7.R.4 Post-marketing investigations" of Review Report (1) and the opinions of the expert advisors in the Expert Discussion.

The applicant explained that specified drug use-results survey would be performed with the planned sample size of 300 patients and 2-year observation period to examine safety in long-term treatment with Mikeluna and safety in combination with other glaucoma drugs.

Based on the above discussion, PMDA concluded that the risk management plan (draft) should include the safety and efficacy specifications listed in Table 12 and the applicant should conduct the additional pharmacovigilance activities and risk minimization activities listed in Table 13.

Table 12. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Asthmatic attack • Syncope • Bradyarrhythmia such as atrioventricular block, sick sinus syndrome, or sinus arrest; congestive heart failure; and vasospastic angina • Iris pigmentation • Corneal epithelium disorder	• Ocular pemphigoid • Cerebral ischemia and cerebrovascular disorders • Systemic lupus erythematosus	None
Efficacy specification		
• Long-term efficacy		

Table 13. Summary of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimizing activities
• Specified drug use-results survey (long-term)	None

Based on the above discussion, PMDA asked the applicant to conduct the post-marketing surveillance to study the above items.

The applicant explained that specified drug use-results survey would be performed in patients with glaucoma and ocular hypertension as indicated in Table 14.

Table 14. Outline of specified drug use-results survey (draft)

Objective	To evaluate long-term safety and efficacy of Mikeluna in clinical use
Survey method	Central registration
Population	Patients with glaucoma and ocular hypertension
Observation period	2 years
Planned sample size	300 patients
Main survey items	• Patient characteristics • Administration status of Mikeluna • Pretreatment and concomitant drugs • Incidence status of adverse events • Clinical Progress (intraocular pressure, anterior ocular findings, visual field, etc.)

PMDA agreed to the above items and considers that the results obtained in the survey should be provided immediately to healthcare professionals in clinical settings.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the conditions indicated below. As the product is a new combination drug, the reexamination period is 6 years. The drug product is not classified as a poisonous drug, a powerful drug, a biological product, or a specified biological product.

Indication

Glaucoma and ocular hypertension

Dosage and Administration

The dosage is one drop of Mikeluna once daily.

Conditions of Approval

The applicant is required to develop and appropriately implement a risk management plan.