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AFFIDAVIT OF TRANSLATION

I, Alan F. Siegrist, of CROSSLINGUAL, LLC, hereby declare that:

1. I am fluent in Japanese and English.
2. I am an active member of the American Translators Association and a Certified Translator of Japanese to English.
3. The English translation attached to this declaration is an accurate and correct translation of the following document, attached hereto:
   Saishin no shinyaku_2001

I declare that the foregoing is true and correct to the best of my knowledge.

Executed on October 26, 2015

Alan F. Siegrist, CT
CROSSLINGUAL, LLC
ATA Member No. 31889
Certification #63788

American Translators Association
ata
Alan F. Siegrist
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A notary public or other officer completing this certificate verifies only the identity of the individual who signed the documents to which this certificate are attached, and not the truthfulness, accuracy, or validity of that document.

State of California, County of CONTRA COSTA

On 10/26/2015 before me, DAVID STURROCK, NOTARY PUBLIC

personally appeared ALAN F. SIEGRIST. who proved to me on the basis of satisfactory evidence to be the person whose name is subscribed to the within instrument and acknowledged to me that he executed the same in his authorized capacity, and that by his signature on the instrument the person, or the entity upon behalf of which the person acted, executed the instrument.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

Witness my hand and official seal.

Signature _____ (Seal)

LS01
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New Drugs in Japan

2001

Yakuji Nippo Edition
Year 2001 Edition

Yakuji Nippo Limited

Preface to "New Drugs in Japan 2001"

During the half-century since 1949, "New Drugs in Japan" has annually collated, edited and published information on newly approved and newly marketed pharmaceuticals (for prescription and non-prescription use) in the broadest possible scope.

On the occasion of the 50th anniversary of the inaugural issue in 2000, the character of a "new drug yearbook" introducing pharmaceuticals newly put on the market during the previous year was more sharply defined, and a new start was made by updating listing methods, classifications, and appearance, as well as enlarging the format to B5-size. "New Drugs in Japan 2001" — the second volume since the relaunch — is an introductory new drug yearbook which collects, classifies, and arranges in the broadest possible scope the new drugs (for prescription and non-prescription use) that were approved and newly marketed during the previous year (2000) within Japan.

The editorial guidelines are as follows.

1. Classification method

Listed pharmaceuticals are broadly classified into: I. pharmaceuticals containing new active ingredients (new substances) (excluding new administration routes and new standards); II. newly marketed prescription drugs (excluding the pharmaceuticals containing new active ingredients of I); and III. non-prescription drugs. Prescription drugs are arranged by pharmacoefficacy classification in conformity with the Japan Standard Commodity Classification (June 1990 Revision), and non-prescription drugs broadly conform to the order of the "Standards for manufacturing (importation) approval of non-prescription drugs" with suitable adjustments.

2. Listing system

With respect to pharmaceuticals containing new active ingredients, not only are package inserts (including reference literature) recorded for the pertinent pharmaceuticals, but also the development background, reexamination period, basis for drug price calculation, and so on.

With respect to other prescription drugs, there is listing of efficacy/effects, usage,/dosage, foreign name of pertinent product, regulation, manufacturing (import sales) origin / sales (marketing) origin, approval date, sales initiation date, date of price listing, price standard listing pharmaceutical code, and packaging, and this is done by unit of generic name classified/arranged in the order of pharmacoefficacy classification.

Beginning with this issue, we have created a page for introducing pharmaceuticals with newly added efficacies (prescription drugs that have been given added efficacy during January-December 2000).

With respect to non-prescription drugs, there is listing of manufacturing (import sales) origin / sales (marketing) origin, approval date, sales initiation date, product characteristics, ingredients and quantities, additives, usage/dosage, and packaging,

3. Descriptive content

"Cautions for use" pertaining to pharmaceuticals containing new active ingredients are in principle recorded as in the description of the package insert, and are omitted with respect to other new drugs. The method of referring to back issues of this publication was discontinued. The so-called commentary which had been included up to the 50th issue is not included in the editing of package insert compliance documentation.

As described above, this publication was created as a "new drug yearbook" of what was newly approved and marketed over a one-year period, and we await the comments and requests of all our readers with respect to this volume.

This volume was edited based on the studies and information gathering conducted by our company with respect to the various pharmaceutical manufacturing / sales (marketing) companies. Hereafter, we will request a still greater number of pharmaceutical companies to cooperate with our studies.

Finally, we would like to express our deep gratitude to all our readers and all the pharmaceutical companies that have cooperated with our studies over this past half-century to the present, and to Tohoku University Honorary Professor Mitsuru Ozawa who has written for us over the half century since the inaugural issue, and who also provided useful advice on the occasion of this edition.

We appeal for the cooperation and support of everyone as we seek to further enhance this publication.

May 2001

Yakuji Nippo Limited

(Remarks)
Product characteristics
(1) It is an ophthalmic solution of Acitazanolast which is an *in vivo* activating metabolite of the oral anti-allergic agent Tazanolast.
(2) Improves subjective and objective symptoms such as pruritus and conjunctival chemosis due to allergic conjunctivitis.
(3) Inhibits release of platelet-activating factors (PAF), histamine, leukotriene B_4, leukotriene D_4 (*in vitro*; rat, guinea pig).

Bromfenac sodium hydrate					
Non-steroidal anti-inflammatory ophthalmic agent				Japan Standard Commodity Classification No.	
				871319	
Bronuck ophthalmic solution – Bronuck (Instructions) (Notations) Senju Pharmaceutical. Co. (manufacture) / Takeda Pharmaceutical Co. (marketing)					
	Approval date	Sales initiation	Drug price listed	Drug price code	Approval No.
	March 10, 2000	July 3, 2000	May 2, 2000	1319743Q1025	21200AMZ00168

[Development Background]

With respect to treatment of ocular inflammation, both steroidal ophthalmic agents and non-steroidal anti-inflammatory drug (NSAID) ophthalmic agents are currently in general use. However, compared to steroidal ophthalmic agents, there are fewer types of NSAID ophthalmic agents, and options are limited. Thus, development of NSAID ophthalmic agents having broad efficacy and strong anti-inflammatory action relative to inflammatory ailments of the external eye and anterior eye is desirable.

Bromfenac sodium hydrate, which is the active ingredient of Bronuck ophthalmic solution, was discovered by the A. H. Robins Co. (now the Wyeth-Ayerst Co.) as a novel NSAID that powerfully inhibits production of prostaglandin which is an inflammatory mediator. By modifying bromine at the 4th position of the benzoyl group of Amfenac, which is the basic skeleton, this drug strives to reinforce anti-inflammatory action and sustain analgesic action.

Focusing on this strong prostaglandin production inhibiting action, Senju Pharmaceutical Co., Ltd. proceeded with development of this drug from 1987. Bronuck ophthalmic solution was approved in March 2000 as a symptomatic therapeutic agent that is effective with two ocular instillations per day with respect to blepharitis, conjunctivitis, scleritis (including episcleritis), and postoperative inflammation.

[Reexamination Period] 6 years

[Contraindications (do not administer to the following patients)]
Patients with a previous history of hypersensitivity to the ingredients of this drug

[Composition / Properties]

Ingredients / content (in 1 ml)	Bromfenac sodium hydrate 1 mg
Additives	Boric acid, borax, dry sodium sulfite, sodium edetate, povidone, polysorbate 80, benzalkonium chloride
Form of drug	Aqueous ophthalmic solution
Color	Clear yellow
pH	8.0–8.6
Other	Aseptic preparation

[Efficacy / Effects]

Symptomatic treatment of inflammatory ailments of the external eye and anterior eye (blepharitis, conjunctivitis, scleritis (including episcleritis), and postoperative inflammation)

[Usage / Dosage]

Ordinarily, 1-2 drops per administration, and 2 ocular instillations per day.

[Cautions for Use]

1. Important Basic Cautions

(1) Keeping in mind that treatment by this drug is symptomatic treatment rather than causal treatment, and that it is reported that serious liver damage (including death) has been observed in patients subjected to long-term administration of 1 month or more with the oral agent of bromfenac sodium, continuous administration for 4 weeks or more is not conducted in principle. Although the aforementioned adverse effects observed with the foreign oral agent were due to long-term administration exceeding the approved usage and dosage, sales have been voluntarily suspended.
(2) As there is risk that eye infection may become subclinical, in case of use on inflammation resulting from infection, administration is to be conducted carefully with adequate observation.

2. Adverse Effects

At the time of approval, adverse effects had been observed in 16 out of a total of 423 cases (3.78%).

With respect to the content of adverse effects, there were 3 cases of blepharitis (0.71%), 3 cases of conjunctival hyperemia (0.71%), 3 cases of stinging (0.71%), 3 cases of ocular pain (temporary) (0.71%), 2 cases of corneal inflammation (0.47%), 1 case of conical epithelial abrasion (0.24%), 1 case of superficial punctate keratitis (0.24%), 1 case of follicular conjunctivitis (0.24%), 1 case of pruritus (0.24%), and l case of burning sensation (eyelids) (0.24%) (at the time of approval).

The following adverse effects were observed in the foregoing study.

0.1% to less than 5%

Ocular* blepharitis, conjunctival hyperemia, stinging, ocular pain (temporary), corneal inflammation, corneal epithelial abrasion, superficial punctate keratitis, follicular conjunctivitis, pruritus, and burning sensation (eyelids)

*When manifested, administration is suspended.

3. Administration to Pregnant, Parturient, and Nursing Women

Administration is to he conducted to pregnant woman or women who may have conceived and to women who are nursing only when it is judged that the benefits of treatment outweigh the risks.

(The safety of administration during pregnancy and lactation has not been established.)

4. Administration to Children

Safety relative to children has not been established (there is little experience with use).

5. Cautions for Use

(1) Administration route: only to be used for ocular instillation

(2) At time of administration: during ocular instillation, take care so that the lip of the container does not directly contact the eye.

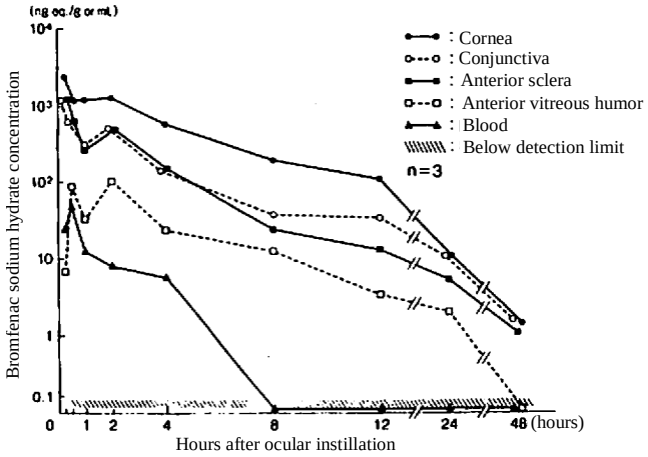
[Pharmacokinetics]

(Reference)

Intraocular Migration <rabbits>[1)]

In testing wherein ocular instillation of 0.05 mL of 0.1% ^{14}C-bromfenac sodium hydrate ophthalmic solution was conducted once a day is both eyes of rabbits, and radioactivity was measured after 15 minutes, 30 minutes, and 1, 2, 4, 8, 32, 24, 48, and 72 hours, elevated values were observed in the cornea, conjunctiva, and anterior sclera.

At 72 hours after ocular instillation, all ocular tissue except for the lens was below the detection limit (0.1 ng eq./g or ml).



[Clinical Results]

A summary of results with respect to 291 cases including double-blind comparative testing are shown in the table.

For the most part, daily dosage and administration period were 1 drop per administration and 2 administrations per day over a 2-week period.

Table. Clinical Effects by Ailment

Name of ailment	Efficacy rate (%) and effectiveness
Blepharitis	66.7 (6/9)
Conjunctivitis	63.2 (60/95)
Scleritis (including episcleritis)	63.6 (7/11)
Postoperative inflammation	86.4 (152/176)
Total	77.3 (225/291)

[Pharmacoefficacy and Pharmacology]

1. Pharmacological Action

(1) Anti-inflammatory action relative to experimental conjunctival chemosis in rats[2)]

It was observed that Bronuck ophthalmic solution exhibited anti-inflammatory action relative to experimental acute conjunctival chemosis in rats induced by arachidonic acid and carageenin.

(2) Inhibitory effects relative to increases in aqueous humor protein concentration in rabbits after anterior chamber paracentesis or after laser irradiation[2)]

It was observed that Bronuck ophthalmic solution almost completely inhibited increases in aqueous humor protein concentration in rabbits after anterior chamber paracentesis or after laser irradiation.

2. Mechanism of Action

In tests using rabbit iris-ciliary bodies[2)] and bovine seminal vesicles, it was confirmed that inhibitory action was exhibited against production of prostaglandin inflammatory mediators via cyclooxygenase (*in vitro*).

[Physicochemical Findings Relative to Active Ingredients]

Generic name: Bromfenac Sodium Hydrate (JAN)

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