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I, Ashley Braun, hereby certify that the following is, to the best of my knowledge and belief, a true and accurate translation of the enclosed documents from Japanese into English:

**“New Drugs in Japan - 2001”**

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Sworn to before me this  
7th day of February 2014

Signature, Notary Public

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# Recent New Drugs 2001

Japanese Pharmacopoeia  
2001 Edition



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Yakuji Nippo Limited

## Preface to “Recent New Drugs 2001”

During the half-century since 1949, “Recent New Drugs” has annually collated, edited and published newly approved and newly marketed pharmaceuticals (for medical and non-prescription uses) in the broadest possible scope.

On the occasion of the 50<sup>th</sup> 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. “Recent New Drugs 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 medical and non-prescription uses) that were approved and newly marketed during the previous year (2000) within Japan.

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 pharmaceuticals for medical use (excluding the pharmaceuticals containing new active ingredients of I); and III. non-prescription pharmaceuticals. Medical-use pharmaceuticals are arranged by pharmacoefficacy classification in conformity with the Japan Standard Commodity Classification (June 1990 Revision), and non-prescription pharmaceuticals broadly conform to the order of the “Standards for manufacturing (importation) approval of non-prescription pharmaceuticals” 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 medical-use pharmaceuticals, 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 (medical-use pharmaceuticals that have been given added efficacy during January-December 2000).

With respect to non-prescription pharmaceuticals, 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 for tracing to back numbers of this publication was discontinued. The so-called commentary up to the 50<sup>th</sup> compilation is not included in the editing of package insert compliance.

As described above, publication was made 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

Acitazanolast hydrate

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|   |  |
|---|--|
| (Remarks)<br>Product characteristics<br>(1) It is an ophthalmic solution of Acitazanolast which is an <i>in vivo</i> activating metabolite of the oral anti-allergic agent Tazanolast.<br>(2) Improves subjective and objective symptoms such | as pruritus and conjunctival chemosis due to allergic conjunctivitis<br>(3) Inhibits release of platelet-activating factors (PAF), histamine, leukotriene B <sub>4</sub> , leukotriene D <sub>4</sub> ( <i>in vitro</i> ; rats, guinea pigs) |
|---|--|

|  |                |                  |   |              |               |
|--|----------------|------------------|---|--------------|---------------|
| 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. (sale) |                |                  |   |              |               |
|  | Approval date  | Sales initiation | Price listing                               | 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 A.H. Robins Co. (now Wyeth-Ayerst Co.) as a novel NSAID that powerfully inhibits production of prostaglandin which is an inflammatory mediator. By modifying bromine at the 4<sup>th</sup> 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. proceeded with development of this drug from 1987. Bronuck ophthalmic solution was approved in March 2000 as a symptomatic therapeutic agent that is effective at two ocular instillations per day with respect to blepharitis, conjunctivitis, scleritis (including episcleritis), and postoperative inflammation.

[Reexamination period] 6 years

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

[Composition / Properties]

|                                 |  |
|---------------------------------|--|
| Ingredients / content (in 1 ml) | Bromfenac sodium hydrate 1 mg  |
| Additives                       | Boric acid, borax, dried sodium sulfite, sodium edetate, povidone, polysorbate 80, benzalkonium chloride |
| Formulation                     | Aqueous ophthalmic agent   |
| 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 of 4 weeks or more is in principle not conducted. 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 inapparent, in case of use on inflammation resulting

from infection, administration is to be conducted carefully with sufficient 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 irritation (0.71%), 3 cases of ocular pain (temporary) (0.71%), 2 cases of corneal inflammation (0.47%), 1 case of corneal epithelial abrasion (0.24%), 1 case of superficial punctate keratitis (0.24%), 1 case of conjunctival follicle (0.24%), 1 case of pruritus (0.24%), and 1 case of heat 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, irritation, ocular pain (temporary), corneal inflammation, corneal epithelial abrasion, superficial punctate keratitis, conjunctival follicle, pruritus, and heat sensation (eyelids)

\*When manifested, administration is suspended.

**3. Administration to pregnant, parturient, and nursing women**

Administration is to be 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 installation

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

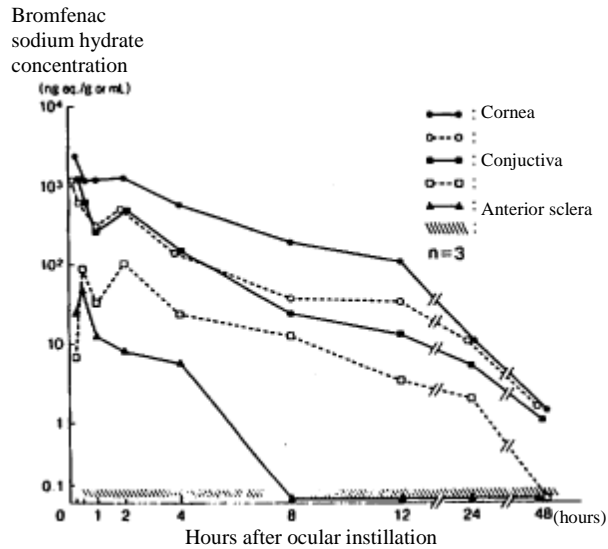
**[Pharmacokinetics]**

(Reference)

Intraocular migration <rabbits><sup>1)</sup>

In testing wherein ocular installation of 0.05 mL of 0.1% <sup>14</sup>C-bromfenac sodium hydrate ophthalmic solution was conducted once a day to both eyes of a rabbit, and radioactivity was measured after 15 minutes, 30 minutes, and 1, 2, 4, 8, 12, 24, 48, and 72 hours, elevated values were observed in the cornea, conjunctiva, and anterior sclera.

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



**[Clinical effects]**

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) Experimental anti-inflammatory action relative to conjunctival chemosis in rats<sup>2)</sup>

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

(2) Inhibitory effects relative to increases in aqueous humor protein concentration in rabbits after anterior chamber paracentesis or after laser irradiation<sup>2)</sup>

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<sup>2)</sup> 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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