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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:
   2000.5 - 1st Edition [Bronuck Package Insert]

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

Executed on October 29, 2015

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

American Translators Association
ata
Alan F. Siegrist
Japanese into English
Certification #63788
Certified Translator

Verify at www.atanet.org/verify

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 October 29, 2015 before me, Jacqueline Wiler Boucher

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 Jacqueline Wiler Boucher (Seal)

JACQUELINE WILER BOUCHER
COMM. #2105829
Notary Public - California
Contra Costa County
My Comm. Expires Apr. 5, 2019

May 2000 – Created (New Format, First Edition)

Storage Method: Room temperature storage
Expiration: To be used by the expiration date displayed on the exterior package (even before expiration, to be used promptly after opening).

Japan Standard Commodity Classification No.	871319
Approval No.	21200AMZ00168
Drug price listed	May 2000
Sales initiation	July 2000
International origin	July 1997

Non-steroidal anti-inflammatory ophthalmic agent

Designated Prescription Drug

BRONUCK® OPHTHALMIC SOLUTION

Bromfenac sodium hydrate ophthalmic solution

[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 1 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 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 instillation

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

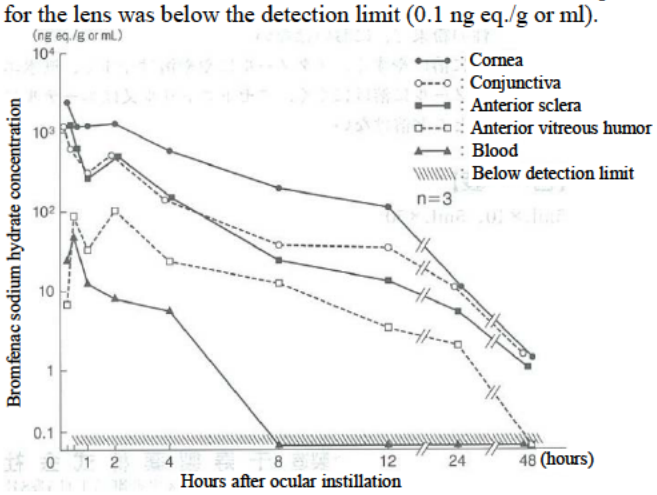
[Pharmacokinetics]

(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]

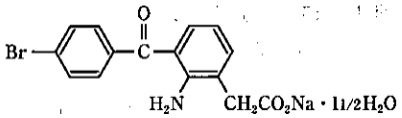
Generic name: Bromfenac Sodium Hydrate (JAN)

Chemical name: sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate

Molecular formula: $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2} H_2O$

Molecular weight: 383.17

Structural formula:



Properties: Bromfenac Sodium Hydrate is an odorless crystalline powder of yellow-orange color. It is freely soluble in water, soluble in methanol, slightly soluble in ethanol anhydride, and practically insoluble in acetonitrile or ether.

[Packaging]

5 mL × 10, 5 mL × 50

[Principal Literature]

1) Mitsuyoshi Isaka *et al.*: Pharmacokinetics, **14** (1) 32, 1999
2) Takahiro Ogawa *et al.*: Journal of Japan Ophthalmology Society, 99, 406, 1995

[Contact for Requesting Literature]

Scientific Information Department
Senju Pharmaceutical Co., Ltd.
5-8, Hirano-machi 2-chome, Chuo-ku, Osaka-shi, Osaka

Manufactured by: Senju Pharmaceutical Co., Ltd.
5-8, Hirano-machi 2-chome,
Chuo-ku, Osaka

Marketed by: Takeda Pharmaceutical Co., Ltd.
1-1, Dosho-machi 4-chome,
Chuo-ku, Osaka

貯　　法：室温保存
使用期限：外箱に表示の使用期限内に使用すること（使用期限内であっても、開封後は速やかに使用すること）。

承認番号	21200AMZ00108
薬価収載	2000年5月
販売開始	2000年7月
国際誕生	1997年7月

非ステロイド性抗炎症点眼剤

指定医薬品

ブロナック®点眼液

BRONUCK® OPHTHALMIC SOLUTION

ブロムフェナクナトリウム 水和物 点眼液

【禁忌（次の患者には投与しないこと）】
本剤の成分に対し過敏症の既往歴のある患者

【組成・性状】

成分・含量（1mL中）	ブロムフェナクナトリウム 水和物 1mg
添加物	ホウ酸、ホウ砂、乾燥亜硫酸ナトリウム、エデト酸ナトリウム、ポビドン、ポリソルベート80、塩化ベンザルコニウム
剤　形	水性点眼剤
色	黄色澄明
pH	8.0～8.6
その他	無菌製剤

【効能・効果】

外眼部及び前眼部の炎症性疾患の対症療法〔眼瞼炎、結膜炎、強膜炎（上強膜炎を含む）、術後炎症〕

【用法・用量】

通常、1回1～2滴、1日2回点眼する。

【使用上の注意】

1. 重要な基本的注意

(1)本剤による治療は原因療法ではなく対症療法であることに留意し、また、外国において、ブロムフェナクナトリウムの経口剤を1ヵ月以上長期投与した患者に重篤な肝障害（死亡を含む）が認められたとの報告があるので、原則として4週間以上の継続投与は行わないこと。なお、外国の経口剤に認められた上記の副作用は承認の用法・用量を超えた長期投与によるものであるが、自主的に販売を中止している。

(2)眼の感染症を不顕性化するおそれがあるので、感染による炎症に対して用いる場合には観察を十分に行い、慎重に投与すること。

2. 副作用

承認時での総症例423例中16例（3.78%）に副作用が認められた。

副作用内容は、眼瞼炎3件（0.71%）、結膜充血3件（0.71%）、刺激感3件（0.71%）、眼痛［一過性］3件（0.71%）、角膜糜爛2件（0.47%）、角膜上皮剥離1件（0.24%）、点状表層角膜炎1件（0.24%）、結膜濾胞1件（0.24%）、瘙痒感1

以下の副作用は上記の調査で認められたものである。

	0.1～5%未満
眼注)	眼瞼炎、結膜充血、刺激感、眼痛［一過性］、角膜糜爛、角膜上皮剥離、点状表層角膜炎、結膜濾胞、瘙痒感、熱感［眼瞼］

注）発現した場合には、投与を中止すること。

3. 妊婦、産婦、授乳婦等への投与

妊婦又は妊娠している可能性のある婦人及び授乳中の婦人には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。

［妊娠中及び授乳中の投与に関する安全性は確立していない。］

4. 小児等への投与

小児等に対する安全性は確立していない（使用経験が少ない）。

5. 適用上の注意

(1)投与経路：点眼用にのみ使用すること。

(2)投 与 時：点眼のとき、容器の先端が直接目に触れないように注意すること。

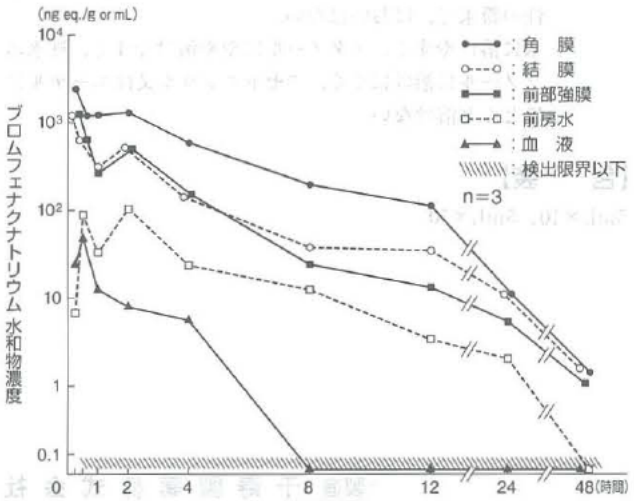
【薬物動態】

（参　考）

眼内移行〈ウサギ〉[1]

ウサギの両眼に0.1%^{14}C-ブロムフェナクナトリウム 水和物 点眼液0.05mLを1回点眼し、15、30分、1、2、4、8、12、24、48、72時間後に放射活性を測定した試験では、角膜、結膜及び前部強膜に高値を示した。

点眼後72時間では、水晶体を除くすべての眼組織で検出限界（0.1ng eq./g or mL）以下であった。



二重盲検比較対照試験を含む291例についての成績概要は表のとおりである。

なお、1日投与量、投与期間は大部分が1回1滴、1日2回、2週間である。

表．疾患別臨床効果

疾患名	有効率(%)有効以上
眼瞼炎	66.7 (6/ 9)
結膜炎	63.2 (60/ 95)
強膜炎 (上強膜炎を含む)	63.6 (7/ 11)
術後炎症	86.4 (152/176)
合計	77.3 (225/291)

【薬効薬理】

1. 薬理作用

(1)ラット実験的結膜浮腫に対する抗炎症作用[2]

ブロナック点眼液はラットにおけるアラキドン酸、カラゲニンによる実験的急性結膜浮腫に対し抗炎症作用を示すことが認められている。

(2)ウサギ前房穿刺後又はレーザー照射後の房水蛋白濃度増加に対する抑制効果[2]

ブロナック点眼液はウサギにおける前房穿刺後又はレーザー照射後の房水蛋白濃度増加をほぼ完全に抑制することが認められている。

2. 作用機序

ウサギ虹彩毛様体[2]及びウシ精嚢を用いた試験において、シクロオキシゲナーゼを介するプロスタグランジン系の炎症メディエーター生成抑制作用を示すことが確認されている(*in vitro*)。

【有効成分に関する理化学的知見】

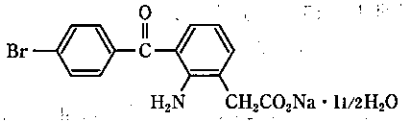
一般名：ブロムフェナクナトリウム 水和物
(Bromfenac Sodium Hydrate)〔JAN〕

化学名：sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate

分子式：$C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2}H_2O$

分子量：383.17

構造式：



性　状：ブロムフェナクナトリウム 水和物は、黄色～橙色の結晶性の粉末で、においはない。
水に溶けやすく、メタノールにやや溶けやすく、無水エタノールに溶けにくく、アセトニトリル又はエーテルにほとんど溶けない。

【包　装】

5mL×10、5mL×50

1) 井坂光良他：薬物動態, 14(1), 32, 1999.
2) 小河貴裕他：日本眼科学会雑誌, 99, 406, 1995.

【文献請求先】

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