ADISINSIGHT (Adis R&D Insight)

Subject Coverage

Weekly reports on new drugs in research, changes in development phases, and licensing availability

File Type

Substance, Full Text

Features

Alerts (SDI)	Weekly				
CAS Registry Number® Identifiers	☑	Page Images	☐	STN® AnaVist™	☐
Keep & Share	☑	SLART	☑	STN Easy®	☑
Learning Database	☐	Structures	☑		

Record Content

- Full text reports, i.e., profiles, on drugs in active research and development by the international pharmaceutical industry
- Generic names, synonyms, trade names
- CAS Registry Numbers®
- EphMRA ATC codes, WHO ATC codes
- Developing companies, development stages by indication and country
- Licensed forecast information from Lehman Brothers
- Adis's own unique therapeutic value rating

File Size

More than 45,730 records (8/19)

Coverage

1998 to the present

Updates

Weekly

Language

English

Database Producer

Springer International Publishing AG
Copyright Holder

Contact Springer Online Services support desk:
Email: onlineservice@springer.com
Phone: +49 6221 345 4303 (Europe/Asia/Africa)
+1 800 777 4643 (North & South America)

Sources

- Direct contact with companies involved with research and development
- 1,700 biomedical and medical journals
- International meetings and conferences
- Company annual reports
- News services
- Press releases
- Licensed Lehman Brothers' PharmaPipelines data

User Aids	• Online Helps (HELP DIRECTORY lists all help messages available) • STNGUIDE
Clusters	• ADISBASES • BIOSCIENCE • CASRNS • COMPANIES • FORMULATION • FULLTEXT • HEALTH • MEDICINE • PHARMACOLOGY • TOXICOLOGY STN Database Clusters information (PDF).
Pricing	Enter HELP COST at an arrow prompt (=>).

Search and Display Field Codes

The following fields that allow left truncation (/BI, /CNS and /RNTE) are marked with an asterisk.

Search Field Name	Search Code	Search Examples	Display Codes
Basic Index* (contains single words from the classification code (CC), development status (DSTA), text (TX), revision note (RNTE), company name (CO), chemical name (CN), controlled term (CT), and geographic term (GT) fields, as well as molecular formulas (MF) and CAS Registry Numbers (RN))	None (or /BI)	S IMMUNOSTIMULANTS S ANTI-ATHER? S GLAXO (L) ORIGINATOR S MECHANISM(L)IMMUNOMODULATORS S C (1W) GO S VACCINE# (P) USE S C10H10N2O5 S 47931-85-1	CC, CN, CO, DSTA, MF, RN, RNTE, TX
Accession Number	/AN	S 1998:9493/AN	AN
Change Date **(1)**	/CDAT	S CDAT>19980100 S JULY 2, 1998/CDAT	CDAT
Chemical Name (includes chemical names, generic names, synonyms, and trade names)	/CN	S POLOXAMER 188 NF/CN	CN
Chemical Name Segment*	/CNS	S (METHYL (L) THIAZOL)/CNS S ?AMINOBUTYRYL?/CNS S (SALBUTAMOL AND SCHERING)/CNS	CN
Classification Code (EphMRA ATC codes and WHO ATC codes) (code and text) **(2)**	/CC	S R03/CC S R3/CC S "ANTI-ACNE PREPARATIONS"/CC S TOPICAL PREPARATIONS/CC	CC
Company Name **(2)** (corporate name and location)	/CO	S SMITHKLINE UNITED KINGDOM/CO S LICENSEE (L) INTROGEN/CO	CO
Controlled Term (indication)	/CT	S ALZHEIMER?/CT S ANXIETY DISORDERS/CT	DSTA
Development Status (development phase, location, and indication)	/DSTA	S (PHASE II (L) GERMANY)/DSTA S (STROKE (L) PRECLINICAL)/DSTA	DSTA
Document Number	/DN	S 002345/DN	DN
Element Count, Specific **(1)**	/Element symbol	S 1/N AND 3/O	MF
Entry Date **(1)**	/ED	S L1 AND ED>=19990700	Not displayed
Field Availability (code and text)	/FA	S EVALUATION/FA S L1 AND RN/FA	FA
Geographic Term (code and text)	/GT	S GERMANY/GT S DE/GT	DSTA
Highest Development Phase	/HDP	S PHASE III/HDP	HDP
Journal Title	/JT	S ADIS R&D INSIGHT/JT	JT, SO
Molecular Formula	/MF	S C10H10N2O5/MF S C18 H22 N2 O S . Cl H/MF	MF
Number of Components **(1)**	/NC	S L6 AND NC>=2	MF
Other Source (Adis Alerts Accession Number)	/OS	S "800007351"/OS	OS
Periodic Group	/PG	S T3/PG	MF
Reference	/RE	S JOURNAL OF PHARMACOLOGY/RE	RE
Revision Date **(1)**	/RDAT	S 19980312/RDAT	RDAT

Search and Display Field Codes (cont'd)

Search Field Name	Search Code	Search Examples	Display Codes
Revision Note*	/RNTE	S PRECLINICAL DEV?/RNTE	RNTE
Source	/SO	S ADIS R&D INSIGHT/SO	SO
Trade Name	/TN	S TANADOPA/TN	CN
Update Date **(1)**	/UP	S L1 AND UP>=19990600	Not displayed
Word Count **(1)**	/WC	S L1 AND WC	WC

(1) Numeric search field that may be searched using numeric operators or ranges.
(2) Implied (S) proximity is available in this field.
(3) This score is only available in selected records published in November 2010 and earlier.

DISPLAY and PRINT Formats

Any combination of formats may be used to display or print answers. Multiple codes must be separated by spaces or commas, e.g., D L1 1-5 CN TX. The fields are displayed or printed in the order requested.

Hit-term highlighting is available for all fields except FA, STF, STR, and STS. Highlighting must be ON during SEARCH in order to use the HIT, KWIC, and OCC formats.

Format	Content	Examples
AN	Accession Number	D AN
CC	Classification Code (EphMRA ATC codes and WHO ATC codes)	D 1-3 CC
CDAT **(1)**	Change Date	D CDAT
CN	Chemical Name (Generic Names, Synonyms, Chemical Name, and Trade Names) (includes TN)	D CN STR
CO	Company Name (corporate name and location) (Originator, Parent, Licensee, and Other)	D CO 1,3-5
DN	Document Number	D AN DN
DSTA	Development Status (development status, location, and indication)	D DSTA
FA **(2)**	Field Availability	D FA
HDP	Highest Development Phase	D HDP
JT **(2)**	Journal Title	D JT 2
MF	Molecular Formula	D CN MF
OS	Other Source (Adis Alerts Accession Number)	D OS
RDAT (RNTE)	Revision Date and Revision Note	D RDAT
RE	Reference	D RE L1 4
RN	CAS Registry Number and Related CAS Registry Number	D RN 3,4
SO	Source	D SO
STF	Flat Structure (no stereo indicated)	D L9 1 3
STR **(3)**	Structure Diagram (includes stereo bonds and R/S/E/Z labels when available)	D L4 STR
STS **(2,3)**	Stereo Structure (includes stereo bonds when available)	D STS
TN **(2)**	Trade Name	D TN
TX	Text (Introduction, Evaluation, Commercial Summary (table with Company, Major Markets, Launch Date, Commercial Value, and Patent Expiry), Pharmacology Overview (Mechanism of action, Route of Elimination), Clinical Overview, Adverse Events, Pharmacology (Pharmacokinetics, Clinical Studies), and Therapeutic Trials) (includes EVAL)	D TX
WC	Word Count	D WC
ALL **(3)**	AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, DSTA, CO, OS, WC, TX, RDAT, RNTE, RE	D ALL
DALL **(3)**	ALL, delimited for post-processing	D DALL
IALL **(3)**	ALL, indented with text labels	D IALL
IDE **(3)**	AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, CO, OS, WC	D IDE
IIDE **(3)**	IDE, indented with text labels (IIDE is the default)	D L2 3 IIDE D
ISTD **(3)**	STD, indented with text labels	D ISTD

DISPLAY and PRINT Formats (cont'd)

Format	Content	Examples
SCAN **(1,4)** STD **(3)** TRIAL **(1)** (SAM, TRI)	CN (Generic Name) (random display, no answer number) AN, SO, DN, CDAT, CN, MF, RN, STR, related RN, CC, HDP, DSTA, CO, OS, WC, TX CN (Generic Name), CDAT	D SCAN D STD D TRIAL TOTAL
HIT KWIC OCC **(1)**	Fields containing hit terms Hit terms with 20 words on either side (KeyWord-In-Context) Number of occurrences of hit terms and fields in which they occur	D HIT D KWIC NOH D OCC

(1) No online display fee for this format.
(2) Custom display format only.
(3) Stereo structure diagrams are available only on graphics terminals and offline prints.
(4) SCAN must be entered on the command line, i.e., DISPLAY SCAN, D SCAN.

SELECT, ANALYZE, and SORT Fields

The SELECT command is used to create E-numbers containing terms taken from the specified field in an answer set.

The ANALYZE command is used to create an L-number containing terms taken from the specified field in an answer set.

The SORT command is used to rearrange the search results in either alphabetic or numeric order of the specified field(s).

Field Name	Field Code	ANALYZE/ SELECT (1)	SORT
Accession Number	AN	Y	N
CAS Registry Number	RN	Y **(2)**	N
CAS Registry Number and Chemical Name	CHEM	Y **(3)**	N
Change Date	CDAT	Y	Y
Chemical Name	CN	Y **(4)** (default)	N
	NAME	Y **(5)**	N
Classification Code (EphMRA and WHO ATC codes)	CC	Y	Y
Company Name (Corporation Name)	CO	Y	Y
Controlled Term (Indication)	CT	Y **(6)**	N
Development Status	DSTA	Y	N
Document Number	DN	Y	Y
Geographic Term	GT	Y **(6)**	N
Highest Development Phase	HDP	Y	Y
Journal Title	JT	Y	Y
Molecular Formula	MF	Y	Y
Occurrence Count of Hit Terms	OCC	N	Y
Other Source (Adis Alerts Accession Number)	OS	Y **(7)**	Y
Reference	RE	Y	N
Revision Date	RDAT	Y **(6)**	N
Revision Note	RNTE	Y **(6)**	N
Source	SO	Y	N
Text	TX	Y **(8)**	N
Trade Name	TN	Y	N
Word Count	WC	N	Y

(1) HIT may be used to restrict terms extracted to terms that match the search expression used to create the answer set, e.g., SEL HIT CN.
(2) Selects or analyzes the CAS Registry for the substance and the related CAS Registry Numbers with /BI appended to the terms created by SELECT.

(3) Selects or analyzes the CAS Registry for the substance, the related CAS Registry Numbers, Generic Names, Synonyms, Chemical Name, and Trade Names) with /BI appended to the terms created by SELECT.
(4) Selects or analyzes the Generic Names, Synonyms, Chemical Name, and Trade Names).
(5) Selects or analyzes the Generic Names, Synonyms, Chemical Name, and Trade Names with /BI appended to the terms created by SELECT.
(6) SELECT HIT and ANALYZE HIT are not valid with this field.
(7) Appends /DN to the terms created by SELECT.
(8) Appends /BI to the terms created by SELECT.

Full-Text Browsing

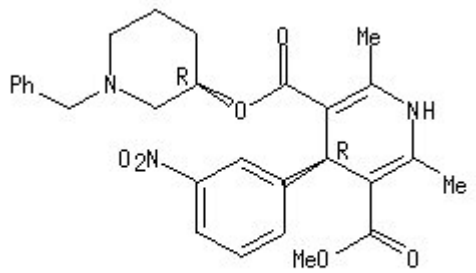
User Request	Example	System Response
DISPLAY BROWSE	=> DISPLAY BROWSE ENTER (L1) OR L#:. ENTER (DIS), ANSWER NUMBERS, OR END:	NOVICE version
D BRO	=> D BRO L1 :	EXPERT version
Answer number(s)	:1-3	display answers 1, 2, and 3 in default format
Answer number(s) and format	:4 HIT	display answer 4 in HIT format
Format only	:TI TX	display title and text of last answer displayed
Change default format	:*KWIC	change default to KWIC no answer displayed
Forward n fields	:F3	move forward 3 fields
Backward n fields	:B1	move backward 1 field
Search forward for character string	:S BONE MARROW	search forward within record for 'bone marrow'
Search backward for character string	:S -NAUSEA	search backward within record for 'nausea'
End DISPLAY BROWSE	:END =>	exit DISPLAY BROWSE and return to => prompt

Sample Records

DISPLAY ALL

AN **1998:1** ADISINSIGHT
SO Adis R&D Insight
DN 000001
CDAT Sep 14, 2016
CN Benidipine
CN Benidipine hydrochloride; KW 3049; KW3049; Nacadipine; Nakadipine
CN 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 1-(phenylmethyl)-3-piperidinyl ester, monohydrochloride, (R*,R*)-(+-)-
CN Caritec(R); Coniel(R)
MF C28 H31 N3 O6 . Cl H
RN 91599-74-5
STR

Relative stereochemistry.



● HCl

RN 105979-17-7 (Benidipine)
CC EPHMRA ATC CODE: C8A Calcium Antagonists, Plain
CC WHO ATC CODE: C08C-A Dihydropyridine derivatives
HDP Launched
DSTA Launched, China, Angina pectoris
Launched, India, Angina pectoris
Launched, Japan, Angina pectoris
Launched, Philippines, Angina pectoris
Launched, Turkey, Angina pectoris
Launched, China, Essential hypertension
Launched, India, Essential hypertension
Launched, Japan, Essential hypertension
Launched, Philippines, Essential hypertension
Launched, Turkey, Essential hypertension
Discontinued III, Italy, Angina pectoris
Discontinued III, Italy, Essential hypertension
Discontinued II, Germany, Angina pectoris
Discontinued II, United Kingdom, Angina pectoris
Discontinued II, United States, Angina pectoris
Discontinued II, Germany, Essential hypertension
Discontinued II, United Kingdom, Essential hypertension
Discontinued II, United States, Essential hypertension
ORIGINATOR: Kyowa Hakko (Japan)
PARENT: Kyowa Hakko
LICENSEE: Bristol-Myers Squibb; Deva Holding; Sun Pharmaceutical Industries
WC 1018

TX TEXT
Introduction:

Company Agreements

In October 2013, Bristol-Myers Squibb licensed the exclusive Chinese marketing rights for benidipine from Kyowa Hakko Kirin. Financial details of the agreement were not disclosed/1/.

Benidipine appears to have been licensed to Deva (an EastPharma subsidiary) for commercialisation in Turkey, and to , Sun Pharmaceutical Industries for commercialisation in India.

Crinos (later Sirton Pharmaceuticals) had licensed benidipine for development in Italy. However, this agreement no longer appears to be active.

In March 2015, Sun Pharmaceutical Industries acquired Ranbaxy/2/.

Introduction

Benidipine is an orally bioavailable dihydropyridine antagonist of L-type, N-type and T-type calcium channels. The drug was developed by Kyowa Hakko (now Kyowa Hakko Kirin) for the treatment of essential hypertension and angina pectoris, and gained approval in Japan in 1991. It has subsequently been launched in Japan, China, Philippines and Turkey (as Coniel sup((R))), and in India (as Caritec sup((R))) for these indications.

In October 2008, Kyowa Hakko merged with Kirin Pharma to form Kyowa Hakko Kirin/3/.

Generic versions of Coniel sup((R)) were launched in Japan in July 2006, following expiry of patent protection in the region.

Key Development Milestones

Benidipine was approved in China in September 2008 for the treatment of angina pectoris, following the filing of an application for regulatory approval in 2007/4/. The drug had been launched in China for the treatment of hypertension in December 2004, after gaining regulatory approval in March 2004. Kyowa Hakko had launched benidipine in the Philippines for both indications by April 2002.

In July 2006, Deva was granted marketing authorisation for benidipine in angina pectoris and essential hypertension, and subsequently launched the product in that country during 2007. Ranbaxy launched the drug in India, in October 2000.

Kyowa Hakko announced in its 2003 annual report that a special investigation evaluating the efficacy and safety of long-term (1 year) administration of benidipine in 10 000 older patients with hypertension had been initiated. A second large-scale clinical trial in collaboration with Yamaguchi University had also been initiated to investigate benidipine in combination with one of three types of antihypertensives (beta-blockers, angiotensin II receptor blockers and antihypertensive diuretics) over a three-year period (COPE; NCT00135551). The effectiveness and safety of the three combination regimens was to be compared and evaluated. This trial enrolled 3501 patients with hypertension in Japan, and was completed in November 2010.

Benidipine was undergoing phase III clinical trials in Italy and phase II trials in Germany, the United Kingdom and the USA for angina pectoris and essential hypertension. However, development appears to have been discontinued in these countries.

TX PHARMACOLOGY OVERVIEW:

Pharmacodynamics:

Coronary and cerebral vasodilatory effects in vivo; marked BP-lowering effects; diuresis; natriuresis

Mechanism of action:

L-type calcium channel antagonists

L-type calcium channel modulators

Calcium channel antagonists

Calcium channel modulators

```
       Ion channel antagonists
        Ion channel modulators
         Membrane glycoprotein inhibitors
          Membrane transport protein inhibitors
           Membrane glycoprotein modulators
            Membrane transport protein modulators
             Glycoprotein inhibitors
              Membrane protein inhibitors
               Carrier protein inhibitors
                Glycoprotein modulators
                 Membrane protein modulators
                  Carrier protein modulators
                   Protein inhibitors
                    Glycoconjugate inhibitors
                     Glycoconjugate modulators
                      Protein modulators
                       Carbohydr-ate metabolism inhibitors

Carboh-ydrate metabolism modulators
 N type calcium channel antagonists
  N-type calcium channel modulators
   Calcium channel antagonists
    Calcium channel modulators
     Ion channel antagonists
      Ion channel modulators
       Membrane glycoprotein inhibitors
        Membrane transport protein inhibitors
         Membrane glycoprotein modulators
          Membrane transport protein modulators
           Glycoprotein inhibitors
            Membrane protein inhibitors
             Carrier protein inhibitors
              Glycoprotein modulators
               Membrane protein modulators
                Carrier protein modulators
                 Protein inhibitors
                  Glycoconjugate inhibitors
                   Glycoconjugate modulators
                    Protein modulators
                     Carbohydr-ate metabolism inhibitors

Carboh-ydrate metabolism modulators
 T type calcium channel antagonists
  T-type calcium channel modulators
   Calcium channel antagonists
    Calcium channel modulators
     Ion channel antagonists
      Ion channel modulators
       Membrane glycoprotein inhibitors
        Membrane transport protein inhibitors
         Membrane glycoprotein modulators
          Membrane transport protein modulators
           Glycoprotein inhibitors
            Membrane protein inhibitors
             Carrier protein inhibitors
              Glycoprotein modulators
               Membrane protein modulators
                Carrier protein modulators
                 Protein inhibitors
                  Glycoconjugate inhibitors
                   Glycoconjugate modulators
                    Protein modulators
                     Carbohydr-ate metabolism inhibitors

Carboh-ydrate metabolism modulators
 Activity versus parent drug:   unspecified parent
```

TX CLINICAL OVERVIEW:
Route(s) of Administration: PO
Adverse events:
rare: Diarrhoea, Oedema.
Drug Interactions:
Unknown.

TX Adverse Events:
In 55 patients with essential hypertension receiving benidipine 2-8 mg/day for <= 1 year, adverse events included lightheadedness (n = 1), diarrhoea (1) and peripheral oedema (1)/5/.

TX PHARMACOLOGY:
Pharmacodynamics (Hypertension):
Preclinical studies: the long term effects of ceronapril 40 mg/kg/day, AE 0047 20 mg/kg/day and benidipine 10 or 20 mg/kg/day were examined in stroke-prone spontaneously hypertensive rats. In treated rats, the incidence of cerebrovascular lesions was significantly depressed and their life-spans were extended compared to the untreated control rats. AE 0047 sustained BP under 210mm Hg without developing fibrinoid deposition on arterial walls. After benidipine, thickened arterial walls were observed and BP remained over 250mm Hg. In contrast to benidipine, ceronapril reduced the occurrence of smooth muscle proliferation and BP levels were similar to those of benidipine/6/.

Clinical studies: a randomised, single-blind, crossover study in 15 salt-sensitive patients with essential hypertension assessed the efficacy of benidipine and controlled release nifedipine on sodium-induced changes in systemic and regional haemodynamics. Oral benidipine 4-8 mg/day once daily for 73 days significantly reduced MAP and increased CI, superior mesenteric blood flow and renal blood flow during low and high sodium intake. Nifedipine 10-30 mg/day also significantly reduced MAP during low sodium intake, but had no effects on HR, CI or regional blood flow. The high sodium diet increased MAP, CI and terminal aortic flow (all $p < 0.05$), and reduced mesenteric and renal blood flows ($p < 0.05$) during nifedipine administration/7/.

In 15 patients with essential hypertension, benidipine 4 mg/day and trandolapril 1 mg/day for 12 weeks similarly decreased BP, and increased concentrations of nitrite/nitrate (NOx) and cGMP. Neither agent affected HR, lipid profiles and renal functions/8/.

In 10 elderly patients with essential hypertension undergoing mental arithmetic test, administration of oral benidipine 4mg od for 12 weeks significantly decreased 24-h BP , and had no marked effect on HR. However, the decrease in night-time DBP was not significant, and the decrease in night-time SBP was minimal. In benidipine recipients, the increase in SBP induced by mental arithmetic test was significantly decreased compared with baseline/9/.

Pharmacodynamics (Ischaemic Heart Disease):
Benidipine suppresses ischaemic ECG changes and attenuates ST and T wave elevation in animal models. Mild and long lasting dose-dependent increases in coronary sinus outflow and decreases in BP are seen at doses > 1 microg/kg IV. Benidipine protects the ischaemic canine myocardium and maintains global cardiohaemodynamics. Other animal studies have shown that benidipine exhibits preferential coronary and cerebral vasodilating activity, and has a longer duration of action than nifedipine or nicardipine.

TX THERAPEUTIC TRIALS:
Hypertension:
In patients with essential hypertension (n = 21), oral once daily benidipine 4 mg/day for 2 weeks produced a long lasting reduction in BP

compared with baseline/10/.

In an open, multicentre study in 78 patients with essential hypertension, monotherapy with oral benidipine 2-8 mg/day od for <= 1 year significantly decreased BP from baseline. Similar effect was achieved when benidipine was used in combination with other antihypertensive agents (n = 19) (details not provided). 42% of patients in the benidipine monotherapy group and 44% of patients in the combination therapy group had their BP normalised at 1 year (BP < 150/90mm Hg)/5/.

In a randomised study in 86 patients with essential hypertension, beta-blockers arotinolol, bisoprolol, ACE inhibitors captopril, imidapril and calcium antagonists nisoldipine and benidipine for 12 weeks significantly and similarly decreased 24h ambulatory BP. 24h HR decreased significantly with the beta-blockers arotinolol and bisoprolol. There were no differences in circadian and ultradian variations among the major first, second and third peaks of SBP, DBP and HR in patients receiving beta-blockers or ACE inhibitors. Calcium antagonists shortened the periodicity of ultradian variations in second and third peaks of SBP/11//9/.

RDAT	RNTE
30 Oct 2000	Launched for Angina pectoris in India (PO)
30 Oct 2000	Launched for Essential hypertension in India (PO)
26 Jan 2000	Two studies have been added to the Hypertension therapeutic trials section (720623, 746001)
05 Jul 1999	Registered for Angina pectoris in India (PO)
05 Jul 1999	Registered for Essential hypertension in India (PO)
30 Apr 1999	A study has been added to the Hypertension pharmacodynamics section (746001)
29 Sep 1998	A study has been added to the Hypertension pharmacodynamics section (691650)
11 Nov 1994	A preclinical study has been added to the hypertension pharmacodynamics section (307950)
14 Sep 1994	New profile

RE
1. Bristol-Myers Squibb. Bristol-Myers Squibb Signs Licensing Agreement for Coniel (benidipine) in China. Media Release. : 22 Oct 2013. Available from: URL: http://www.bms.com.cn. (English).
2. Sun Pharmaceutical Industries. Sun Pharma announces closure of merger deal with Ranbaxy. Media Release. : 25 Mar 2015. Available from: URL: http://www.sunpharma.com. (English).
3. Kyowa Hakko Kogyo Co Ltd, Kirin Pharma Company Limited, et al. Strategic Alliance Between Kyowa Hakko Group and Kirin Group Maximizing Synergy Through an Alliance Centered Around the Pharmaceutical Business. Media Release. : 22 Oct 2007. Available from: URL: http://www.kyowa.co.jp. (English).
4. Kyowa Hakko Kogyo Co Ltd. Kyowa Hakko Interim Operating Income up 25.2%. Media Release. : 29 Oct 2007. Available from: URL: http://www.kyowa.co.jp. (English).
5. Imazu M, Yamabe T, et al. Antihypertensive effects and safety of long-term treatment with benidipine hydrochloride in essential hypertensive patients. Shinryo to Shinyaku. 32: 995-1005, 1995. (Japanese).
6. Ohta Y, Chikugo T, et al. Long term therapeutic effects of ACE inhibitor and calcium antagonists on hypertensive vascular lesions in M-SHRSP. Clinical and Experimental Pharmacology and Physiology. (Suppl. 1): 103, 1994. (English).
7. Shimamoto H, Shimamoto Y. Benidipine counteracts sodium-induced alterations in systemic and regional hemodynamics. Blood Pressure. 6: 18-23, Jan 1997. (English).
8. Takase H, Sugiyama M, et al. Effect of antihypertensive therapy with benidipine or trandolapril on serum nitrite/nitrate levels in essential hypertension. Journal of Hypertension. 16 (Suppl. 2): 99, Jun 1998. (English).
9. Muneta S, Kohara K, et al. Effects of benidipine hydrochloride on

24-hour blood pressure and blood pressure response to mental stress in elderly patients with essential hypertension. International Journal of Clinical Pharmacology and Therapeutics. 37: 141-147, Mar 1999. (English).

10. Nakanishi T, Takahashi H, et al. Effects of benidipine hydrochloride on 24-hour blood pressure. Current Therapeutic Research - Clinical and Experimental. 53: 270-276, Mar 1993. (English).
11. Kawamura H, Mitsubayashi H, et al. Calcium channel blockers shorten the periodicity of ultradian variation in blood pressure in patients with essential hypertension. Koketsuatsu. 21: 179-186, Sep 1998. (English).

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