Bristol-Myers Squibb Company
Attention: Mary E. Norvitch, Ph.D.
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Norvitch:

Please refer to your supplemental new drug applications dated May 18, 2000, received May 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Avapro (irbesartan) 75, 150 and 300 mg Tablets and Avalide (irbesartan/hydrochlorothiazide) 75/12.5, 150/12.5 and 300/12.5 mg Tablets.

We acknowledge receipt of your submissions dated August 15, 2000.

These supplemental new drug applications provide for final printed labeling revised to read as follows:

NDA 20-757 (Avapro-Irbesartan)

ADVERSE REACTIONS, Post-Marketing Experience subsection:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; jaundice.

Hyperkalemia has been rarely reported.

NDA 20-758 (Avalide-Irbesartan/Hydrochlorothiazide)

ADVERSE REACTIONS, Post-Marketing Experience subsection:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue). Hyperkalemia has been rarely reported.

Very rare cases of jaundice have been reported with irbesartan.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert included in your submissions of August 15, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.
If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Edward Fromm
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

RX 9/20/10
cc:
Archival NDAs 20-757, 20-758
HFD-110/Div. Files
HFD-110/E.Fromm
HFD-110/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT
HFD-093/DDMS-IST (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: ef/September 7, 2000
Initialed by: R Mittal/9/8/00
K Srinivasachar/9/8/00
G Jagadeesh/9/8/00
N Stockbridge/9/12/00
N Morgenstern/9/12/00

Final: asb/9/13/00
Filename: 20-758(ap).doc

APPROVAL (AP)
DESCRIPTION

AVAPRO® (irbesartan) is an angiotensin II receptor (AT1 subtype) antagonist.

Irbesartan is a non-peptide compound, chemically described as a 2-butyryl-3-[2-[(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-ylmethyl]-1,3-diazaspiro[4,4]non-1-en-4-one. Its empirical formula is C29H31N2O, and the structural formula:

\[
\text{\includegraphics[width=2cm]{structural_formula.png}}
\]

Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.

AVAPRO is available for oral administration in unscored tablets containing 75 mg, 150 mg, or 300 mg of irbesartan. Inactive ingredients include: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT1 receptors with a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT2 receptor and no agonist activity.

Blockade of the AT1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not affect the response to bradykinin; whether this has clinical relevance is not known.

Pharmacokinetics

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 50–80%. Following oral administration of AVAPRO, peak plasma concentrations of irbesartan are attained at 1.5–2 hours after dosing. Food does not affect the bioavailability of AVAPRO.

Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range.

The terminal elimination half-life of irbesartan averaged 11–15 hours. Steady-state concentrations are achieved within 3 days. Limited accumulation of irbesartan (≤20%) is observed in plasma upon repeated once-daily dosing.

Metabolism and Elimination

Irbesartan is metabolized via glucuronidation and oxidation. Following oral or intravenous administration of 14C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to irbesartan's pharmacologic activity.

Irbesartan and its metabolites are excreted by both biliary and renal routes. Following either oral or intravenous administration of 14C-labeled irbesartan, about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by CYP2C; metabolism by CYP4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2C19). There was no induction or inhibition of CYP450.

Distribution

Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average

*Registered trademark of Sanofi-Synthelabo
Once-daily administration of therapeutic doses of isradipin gave peak effects at around 3–6 hours and, in one ambulatory blood pressure monitoring study, again at 14–18 hours. This was seen with both once-daily and twice-daily dosing. Trough-to-peak ratios for systolic and diastolic response were generally between 60–70%. In a continuous ambulatory blood pressure monitoring study, once-daily dosing with 150 mg gave trough and mean 24-hour responses similar to those observed in patients receiving twice-daily dosing at the same total daily dose. In controlled trials, the addition of isradipin to hydralazine or nifedipine dosages of 6.25, 12.5, or 25 mg produced further dose-related reductions in blood pressure similar to those achieved with the same monotherapy dose of isradipin. HCTZ also had an approximately additive effect.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses. Isradipin was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population).

The effect of isradipin is apparent after the first dose and it is close to its full observed effect at 2 weeks. At the end of an 8-week exposure, about 2/3 of the antihypertensive effect was still present one week after the last dose. Rebound hypertension was not observed. There was essentially no change in average heart rate in isradipin-treated patients in controlled trials.

INDICATIONS AND USAGE

AVAPRO (isradipin) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

AVAPRO is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, AVAPRO should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformations, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers and their embryos are susceptible to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of AVAPRO as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, AVAPRO should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profile (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, it should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

When pregnant rats were treated with isradipin from day 0 to day 20 of gestation (oral doses of 50, 150, and 450 mg/kg/day), increased incidences of renal pelvic caviation, hydronephrosis and/or absence of renal papilla were observed. In fetuses at doses ≥50 mg/kg/day [approximately equivalent to the maximum recommended human dose (MRHD), 300 mg/day, on a body surface area basis]. Subcutaneous edema was observed in fetuses at doses ≥180 mg/kg/day (about 4 times the MRHD on a body surface area basis). As these anomalies were noted in rats in which isradipin exposure (oral doses of 50, 150, and 450 mg/kg/day) was limited to gestation days 6–15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg isradipin/kg/day were associated with maternal mortality and abortion. Surviving females receiving this dose (about 1.5 times the MRHD on a body surface area basis) had a slight increase in early resorptions and a corresponding decrease in live fetuses. Isradipin was found to cross the placental barrier in rats and rabbits.
Radioactivity was present in the rat and rabbit fetus during late gestation and in rat milk following oral doses of radiolabeled isibrsartan.

**Hypotension in Volume- or Salt-depleted Patients**

Excessive reduction of blood pressure was rarely seen (<0.1%) in patients with uncomplicated hypertension; limitation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, e.g., in patients treated vigorously with diuretics or in patients on dialysis. Such volume depletion should be corrected prior to administration of APRO (isibrsartan), or a low starting dose should be used (see DOSAGE AND ADMINISTRATION).

If hypotensive reaction occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

**PRECAUTIONS**

**Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. APRO would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN can be expected. There has been no known use of APRO in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

**Information for Patients**

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Drug Interactions**

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, and nitronepine.

In vitro studies show significant inhibition of the formation of oxidized isibrsartan metabolites with a known cytochrome P450 2C9 substrates/inhibitors sulphonamide, tobutamide and nitronepine. However, in clinical studies the consequences of concomitant isibrsartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes 1A1, 1A2, 2A6, 2B6, 2D6, 2E1, or 3A4.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, isibrsartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of isibrsartan were not affected by coadministration of nitronepine or hydrochlorothiazide.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

No evidence of carcinogenicity was observed when isibrsartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to two years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to isibrsartan (AUC0-24h, bound plus unbound) about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (1200 mg) isibrsartan/day, whereas 1000 mg/kg/day (administrated to females only) provided an average systemic exposure about 21 times that reported for humans at the MDR. For male and female mice, 1000 mg/kg/day provided an exposure to isibrsartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Isibrsartan was not mutagenic in a battery of in vitro tests (Ames microbial test, rat hepatocyte mutagenicity test, V79 Chinese hamster cell forward gene-mutation assay). Isibrsartan was negative in several tests for induction of chromosome aberrations (in vitro human lymphocyte assay; in vivo mouse micronucleus study).

Isibrsartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤50 mg/kg/day, the highest dose providing a systemic exposure to isibrsartan (AUC0-24h, bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

**Pregnancy**

**Pregnancy Categories C (first trimester) and D (second and third trimester).**

**See WARNINGS:** Fetal/Neonatal Morbidity and Mortality

**Nursing Mothers**

It is not known whether isibrsartan is excreted in human milk, but isibrsartan or some metabolite of isibrsartan is secreted at low concentration in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Of the total number of patients receiving APRO (isibrsartan) in controlled clinical studies, 911 patients (18.5%) were 65 years and over, while 150 patients (3.0%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**ADVERSE REACTIONS**

APRO has been evaluated for safety in more than 4300 patients with hypertension and about 5000 subjects overall. This experience includes 1303 patients treated for over 6 months and 407 patients for 1 year or more. Treatment with APRO was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of APRO.

In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3 percent of patients treated with APRO, versus 4.5 percent of patients given placebo.

In placebo-controlled clinical trials, the adverse event experiences that occurred in at least 1% of patients treated with APRO (n=1965) and at a higher incidence versus placebo (n=541) included diarrhea (3% vs. 2%), dyspepsia/heartburn (2% vs. 1%), musculoskeletal trauma (2% vs. 1%), fatigue (4% vs. 3%), and upper respiratory infection (9% vs. 6%). None of these differences were significant.

The following adverse events occurred at an incidence of 1% or greater in patients treated with isibrsartan, but were at least as frequent or more frequent in patients receiving placebo: abdominal pain, anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculoskeletal pain, pharyngitis, nausea/vomiting, rhinitis, sinus abnormalities, tachycardia, and urinary tract infection.

Isibrsartan use was not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitor use. In placebo-controlled studies, the incidence of cough in isibrsartan treated patients was 2.8% versus 2.7% in patients receiving placebo.

The incidence of hypotension or orthostatic hypotension was low in isibrsartan treated patients (0.4%), unrelated to dosage, and similar to the incidence among placebo treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving isibrsartan compared with placebo.

In addition, the following potentially important events occurred in less than 1% of the 1965 patients and at least 5 patients (0.3%) receiving isibrsartan in clinical studies, and those less frequent, clinically significant events (listed by body system).

It cannot be determined whether these events were causally related to isibrsartan: Body as a Whole: fever, chills, facial edema, superior extremity edema; Cardiovascular: flushing, hypertension, cardiac murmur, myocardial infarction, angina pectoris, arrhythmia/conduction disorder, cardiac/respiratory arrest, heart failure, hypertensive crisis; Dermatologic: pruritus, dermatitis, ecchymosis, erythema face, urticaria; Endocrine/Metabolic/Electrolyte imbalances: sexual dysfunction, libido change, gynecomastia; Gastrointestinal: constipation, oral lesion, gastroenteritis, flatulence, abdominal distention; Musculoskeletal/Connective Tissue: extremity swelling, muscle cramp, arthralgia, muscle ache, musculoskeletal chest pain, joint stiffness, bursitis, muscle weakness; Nervous System: sleep disturbance, numbness, somnolence, emotional disturbance, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident; Renal/Goutnourary: abnormal urination, prostate disease; Respiratory: epistaxis, tracheobronchitis, congestion, pulmonary congestion, dyspnea, wheezing; Special Senses: vision disturbance, hearing abnormality, ear infection, ear pain, conjunctivitis, other eye disturbance, eyelid abnormality, ear abnormality; Post-Marketing Experience

The following have been very rarely reported in post-marketing experience: urticaria, angioedema (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; jaundice. Hypersensitivity has been rarely reported.

**Laboratory Test Findings**

In controlled clinical trials, clinically important differences in laboratory tests were rarely associated with administration of APRO.

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with APRO alone versus 0.9% on placebo. (See PRECAUTIONS: Impaired Renal Function).

**Hematology:** Mean decreases in hemoglobin of 0.2 g/dl were observed in 0.2% of patients receiving APRO compared to 0.3% of placebo treated patients. Neutropenia (<1000 cells/mm3) occurred at similar frequencies among patients receiving APRO (0.3%) and placebo treated patients (0.5%).

**OVERTHEROSAGE**

No data are available in regard to overdose in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdose are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Isibrsartan is not removed by hemodialysis.
To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians’ Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient.

Laboratory determinations of serum levels of irbesartan are not widely available, and such determinations have, in any event, no known established role in the management of irbesartan overdose.

Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg) on a mg/m² basis, respectively.

**DOSAGE AND ADMINISTRATION**

The recommended initial dose of AVAPRO is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A low dose of a diuretic may be added, if blood pressure is not controlled by AVAPRO alone. Hydrochlorothiazide has been shown to have an additive effect (see **CLINICAL PHARMACOLOGY**: Clinical Studies). Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing.

No dosage adjustment is necessary in elderly patients, or in patients with hepatic impairment or mild to severe renal impairment.

AVAPRO may be administered with other antihypertensive agents.

AVAPRO may be administered with or without food.

**Volume- and Salt-depleted Patients**

A lower initial dose of AVAPRO (75 mg) is recommended in patients with depletion of intravascular volume or salt (e.g., patients treated vigorously with diuretics or on hemodialysis) (see **WARNINGS**: Hypotension in Volume- or Salt-depleted Patients).

**HOW SUPPLIED**

AVAPRO® (irbesartan) is available as white to off-white biconvex oval tablets, debossed with a heart shape on one side and a portion of the NDC code on the other. Unit-of-use bottles contain 30, 90, or 500 tablets and blister packs contain 100 tablets, as follows:

<table>
<thead>
<tr>
<th>75 mg</th>
<th>150 mg</th>
<th>300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debossing</td>
<td>2771</td>
<td>2772</td>
</tr>
<tr>
<td>Bottle of 30</td>
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<td>0087-2772-31</td>
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<tr>
<td>Bottle of 90</td>
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<tr>
<td>Bottle of 500</td>
<td>0087-2772-15</td>
<td>0087-2773-15</td>
</tr>
<tr>
<td>Blister of 100</td>
<td>0087-2771-35</td>
<td>0087-2772-35</td>
</tr>
</tbody>
</table>

**Storage**

Store at a temperature between 15°C and 30°C (59°F and 86°F) (USP).
CSO Review of Final Printed Labeling

Application: NDA 20-757/S-017
               NDA 20-758/S-018

Applicant: Bristol-Myers Squibb

Document Dates: May 18, 2000 (S-017 & S-018)

Receipt Dates: May 19, 2000 (S-017 & S-018)

Product Names: Avapro (irbesartan) Tablets, 75, 150, 300 mg
               Avalide (irbesartan/hydrochlorothiazide) Tablets, 75/12.5, 150/12.5, 300/12.5 mg

Background: These supplemental applications were submitted in response to our supplement request letter of November 29, 1999 and fax of December 6, 1999 that asked the sponsor to add increased LFT’s and jaundice to the list of adverse reactions associated with irbesartan use.

Review: The sponsor, in a May 18, 2000 submission, sent in draft labeling revised as follows:

NDA 20-757 (Avapro-Irbesartan)

Under ADVERSE REACTIONS, the Post-Marketing Experience subsection has been changed from:

The following adverse reactions have been reported in post-marketing experience: Rare cases of urticaria and angioedema (involving swelling of the face, lips, pharynx, and/or tongue); hyperkalemia.

To:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; jaundice; and hyperkalemia.

NDA 20-758 (Avalide-Irbesartan/Hydrochlorothiazide)

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To:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue); and hyperkalemia.

Very rare cases of jaundice have been reported with irbesartan.
Comments/Recommendations: Dr. Stockbridge found the proposed changes to be acceptable with the exception of hyperkalemia being noted as "very rarely reported". I asked the sponsor on June 1, 2000 to reword the paragraph so that hyperkalemia was "rarely reported", as in the previously approved package insert.

Bristol-Myers Squibb, on June 28, 2000, sent in, by e-mail, revised wording as follows:

NDA 20-757 (Avapro-Irbesartan)

ADVERSE REACTIONS, Post-Marketing Experience subsection:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue); increased liver function tests; jaundice.

Hyperkalemia has been rarely reported.

NDA 20-758 (Avalide-Irbesartan/Hydrochlorothiazide)

ADVERSE REACTIONS, Post-Marketing Experience subsection:

The following have been very rarely reported in post-marketing experience: urticaria; angioedema (involving swelling of the face, lips, pharynx, and/or tongue).

Hyperkalemia has been rarely reported.

Very rare cases of jaundice have been reported with irbesartan.

Dr. Stockbridge said the revised wording pertaining to hyperkalemia was acceptable. I informed the sponsor, on July 10, 2000, of Dr. Stockbridge's acceptance of the revised text and asked them to submit final printed labeling for both Avapro and Avalide. Bristol-Myers Squibb submitted final printed labeling for both drugs on August 15, 2000.

Other changes-NDA 20-757 (Avapro-Irbesartan)

Under HOW SUPPLIED, the unit-of-use bottle containing 500 tablets for the 75 mg strength and the blister pack of 100 tablets for the 300 mg strength of irbesartan have been discontinued. I confirmed this with the sponsor on September 6, 2000 and reminded them to make note of these changes in their next annual report.

There are no other changes from the last approved package inserts.

I will draft an approval letter for Dr. Lipicky's signature.

Edward Fromm
Consumer Safety Officer

Ef-9/07/00
cc: NDA 20-757, 20-758
    HFD-2
    HFD-110
    HFD-110/EFronn
    HFD-110/Blount