1. Product and Company Identification

PRODUCT NAME: AVALIDE® (irbesartan-hydrochlorothiazide) Tablets
150/12.5 mg, 300/12.5 mg

Substance names: Irbesartan, hydrochlorothiazide

Supplier:
Sanofi-aventis U.S. LLC
A SANOFI COMPANY
55 Corporate Drive
Bridgewater, NJ 08807

24-Hour Transport Emergency, US (Chemtrec):	**(800) 424-9300**
24-Hour Transport Emergency, outside US (Chemtrec):	**(703) 527-3887**
US Customer Service	**(800) 207-8049**
24-Hour Emergency, sanofi-aventis US:	**(908) 981-5550**

Product use: Pharmaceutical product.

2. Hazards Identification

2.1 Classification in accordance with 29 CFR 1910.1200

Classification of the finished drug product is not required according to OSHA 29 CFR 1910.1200. The following information is provided for the drug substance, irbesartan:

Classification:
Reproductive toxicity, Category 2
Effects on or via lactation
Specific target organ toxicity - repeated exposure, Category 2

Hydrochlorothiazide is not classified as a hazardous substance.

2.2 Label elements in accordance with 29 CFR 1910.1200

Labeling of the finished drug product is not required according to OSHA 29 CFR 1910.1200. The following information is provided for the drug substance, irbesartan:

Signal Word: Warning

Hazard Statement(s): Suspected of damaging fertility or the unborn child. May cause harm to breast-fed children. May cause damage to kidneys through prolonged or repeated exposure if swallowed.

Symbol(s): Health hazard

Precautionary Statement(s):

- Prevention: Obtain special instructions before use. Avoid contact during pregnancy/while nursing. Do not handle until all safety precautions have been read and understood. Wear protective gloves. Do not breathe dust. Wash hands thoroughly after handling. Do not eat, drink or smoke while using this product.

- Response: If exposed or concerned: Get medical attention.

- Storage: Store locked up.

- Disposal: Dispose of in accordance with applicable regional, national and local laws and regulations.

2.3 Hazards Not Otherwise Classified (HNOC)

Not classified.

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3. Composition/Information on Ingredients

Chemical Name:	**Common Name:**	**CAS #:**	**Percentage or concentration range**
2-butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one	Irbesartan	138402-11-6	150 or 300 mg per tablet
6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide	Hydrochlorothiazide	58-93-5	12.5 mg per tablet

Inactive Ingredients: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, magnesium stearate, silicon dioxide, ferric oxide red, ferric oxide yellow, polyethylene glycol, titanium dioxide, and carnauba wax.

4. First Aid Measures

4.1 First aid procedures

Eye contact: In case of contact with dust from broken tablets or capsules, immediately flush eyes with plenty of water for at least 15 minutes. If easy to do, remove contact lenses if worn. Get medical attention.

Skin contact: In case of contact with broken tablets or capsules, immediately flush skin with plenty of water. Remove contaminated clothing and shoes. Get medical attention if irritation develops and persists.

Ingestion: If swallowed, call a poison center or physician immediately. Do NOT induce vomiting unless directed to do so by a physician. Never give anything by mouth to an unconscious person. Rinse mouth thoroughly with water.

Inhalation: If dust from broken tablets or capsules is inhaled, remove to fresh air. If breathing is difficult, trained personnel should give oxygen. Get medical attention.

4.2 Most important symptoms and effects, both acute and delayed

Hypotension, dehydration; dizziness, drowsiness, insomnia, being tired, rash, diarrhea, vomiting, headache, back or leg pain, muscle cramps, lightheadedness.

4.3 Indication of any immediate medical attention and special treatment needed

Treat symptomatically and supportively.

5. Fire Fighting Measures

5.1 Extinguishing media

Suitable extinguishing media: All means: water, carbon dioxide, foam or dry chemical.

Unsuitable extinguishing media: Strong water jet.

5.2 Specific hazards arising from the chemical

Hazardous combustion products: Carbon monoxide, carbon dioxide, oxides of sulfur and nitrogen.

5.3 Special Protective Equipment and Precautions for Fire-fighters

In case of fire, use full firefighting turnout (bunker) gear and self-contained breathing apparatus (SCBA). Keep personnel upwind and away from fire. Move container from fire area if you can do it without risk. Do not scatter spilled material with high-pressure water streams. Dike fire-control water for later disposal.

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6. Accidental Release Measures

6.1 Personal precautions and Protective Equipment:

Eye protection, respiratory protective equipment, and suitable protective clothing should be worn if significant dust emissions are generated from broken or crushed tablets or capsules.

6.2 Emergency Procedures:

Follow local workplace procedures. Prevent the product from entering the environment. Avoid discharges to sewers, drains, waterways, or onto the ground.

6.3 Methods for containment:

Vacuum or scoop up, moisten any dust with water before collection with a shovel or broom.

6.4 Methods for clean-up:

Place material in suitable container for disposal. Wash the floor with plenty of water, absorb or retain the cleaning water for disposal.

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7. Handling and Storage

7.1 Precautions for Safe Handling

Use with adequate ventilation. Avoid breathing dust if tablets are crushed or spilled. Do not get dust in eyes or on skin. Wash thoroughly after handling.

7.2 Conditions for Safe Storage

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F).

8. Exposure Controls/Personal Protection

8.1 Exposure Limits

Sanofi-aventis occupational exposure limit, irbesartan: 0.1 mg/m^3, 8-hour TWA.

Sanofi-aventis occupational exposure limit, hydrochlorothiazide: 0.085 mg/m3, 8-hour TWA.

8.2 Appropriate Engineering Controls

Provide adequate ventilation. No other specific controls are needed under normal handling conditions.

8.3 Individual Protection Measures

Eye/face protection: Safety glasses or safety goggles should be worn if there is a potential for dust exposure from broken or crushed tablets.

Skin protection: Suitable protective gloves should be worn if handling the unfinished product or broken or crushed tablets.

Respiratory protection: None normally required. Approved respiratory protection should be worn if there is a potential for exposure to dust from handling operations or from broken or crushed tablets.

General hygiene considerations: Suitable work clothes. Wash hands before breaks and at the end of the work shift.

9. Physical and Chemical Properties

Appearance: Peach-colored, oval-shaped tablets.
Odor: None
Odor threshold: Not applicable.
pH: Not available.
Melting point/ Freezing point: Not applicable.
Initial boiling point/boiling point range: Not applicable.
Flash point: Not applicable.
Evaporation rate: Not applicable.
Flammability: Not available.
Upper/lower flammability or explosive limits: Not available.
Vapor pressure: Not applicable.
Vapor density: Not applicable.

Relative density: Not available.
Solubility: Not available.
Partition coefficient: n-octanol/water:
Irbesartan: Log Kow = 1.13 at pH 7 (measured);
Hydrochlorothiazide: Log Kow = - 0.1 (calculated)
Auto-ignition temperature: Not available.
Decomposition temperature: Not available.
Viscosity: Not available.

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10. Stability and Reactivity

10.1 Reactivity

Not a reactive material under normal handling conditions.

10.2 Chemical Stability

Stable under normal handling conditions.

10.3 Possibility of hazardous reactions

None known.

10.4 Conditions to Avoid

Keep away from heat, sparks and flames.

10.5 Incompatible materials

Strong oxidizing and reducing agents.

10.6 Hazardous decomposition products

Carbon monoxide, carbon dioxide, oxides of sulfur and nitrogen.

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11. Toxicological Information

The following information is for the active ingredient irbesartan unless otherwise noted:

Information on likely routes of exposure: Exposure not expected under normal use. Dust from broken or crushed tablets could result in exposure to eyes, skin and respiratory tract.

Symptoms related to the physical, chemical and toxicological characteristics: Hypotension, dehydration; dizziness, drowsiness, insomnia, being tired, rash, diarrhea, vomiting, headache, back or leg pain, muscle cramps, lightheadedness.

Effects of short-term (acute) exposure: Electrolyte imbalance. Increased levels of blood potassium levels.

Effects of long-term (chronic) exposure: Potential for kidney damage based on animal studies.

Acute toxicity (LD50):
Irbesartan: Oral route, rat: > 2,000 mg/kg
Hydrochlorothiazide: Oral route, rat: 2,750 mg/kg

Skin corrosion/irritation: Not a skin irritant.

Serious eye damage/irritation: Not an eye irritant.

Sensitization: Not a dermal sensitizer.

Specific target organ toxicity – single exposure (STOT-SE): No data available.

Specific target organ toxicity – repeated exposure (STOT-RE): In a 6-month study in monkeys, dose-related hyperplasia of juxtaglomerular apparatus was observed in all treated animals, it was partially reversible at the end of treatment. LOEL = 10 mg/kg/day.

Carcinogenicity: No evidence of carcinogenicity was observed when irbesartan 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 2 years.

Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Irbesartan-Hydrochlorothiazide: No carcinogenicity studies have been conducted with the irbesartan-hydrochlorothiazide combination.

Not listed by NTP, not found to be a potential carcinogen by IARC or OSHA.

Titanium dioxide has been classified by IARC as 2B: Possibly carcinogenic to humans. Tumors were observed at high dose in animal studies by inhalation and intratracheal administration. Tumors were not observed by other routes.

Reproductive toxicity and teratogenicity: Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death.

When pregnant rats were treated with irbesartan from day 0 to day 20 of gestation (oral doses of 50 mg/kg/day, 180 mg/kg/day, and 650 mg/kg/day), increased incidences of renal pelvic cavitation, hydroureter 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 not observed in rats in which irbesartan exposure (oral doses of 50, 150, and 450 mg/kg/day) was limited to gestation days 6 to 15, they appear to reflect late gestational effects of the drug. In pregnant rabbits, oral doses of 30 mg irbesartan/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. Irbesartan was found to cross the placental barrier in rats and rabbits.

Mutagenicity: Irbesartan was not mutagenic in a battery of in vitro tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (in vitro-human lymphocyte assay; in vivo-mouse micronucleus study).

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene.

Irbesartan-hydrochlorothiazide was not mutagenic in standard in vitro tests (Ames microbial test and Chinese hamster mammalian-cell forward gene-mutation assay). Irbesartan-hydrochlorothiazide was negative in tests for induction of chromosomal aberrations (in vitro—human lymphocyte assay; in vivo—mouse micronucleus study).

Aspiration hazard: Not applicable.

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12. Ecological Information

The following information is for the active ingredient irbesartan unless otherwise noted:

12.1. Ecotoxicity

Fish toxicity (LC50): > 290 mg/l
Species: Oncorhynchus mykiss (rainbow trout)
Exposure duration: 96 h

Chronic aquatic toxicity (NOEC): 7.04 mg/l
Species: Pimephales promelas

Toxicity on invertebrates (EC50): 191 mg/l
Species: Daphnia magna
Exposure duration: 48 h

Toxicity on invertebrates (Chronic toxicity) (NOEC): 10.4 mg/l
Species: Daphnia magna
Algae toxicity (EbC50): 79 mg/l
Species: Pseudokirchneriella subcapitata (green algae)
Exposure duration: 72 h
Endpoint: Biomass

Algae toxicity (ErC50): 460 mg/l
Species: Pseudokirchneriella subcapitata (green algae)
Exposure duration: 72 h
Endpoint: Growth rate

Bacteria toxicity (EC50): > 1,000 mg/l
Species: Activated sludge
Exposure duration: 3 h

The following information is for the active ingredient hydrochlorothiazide:

Fish toxicity (LC50): > 100 mg/l
Species: Brachidanio rerio
Exposure duration: 96 h
Method: OECD 203

Chronic aquatic toxicity: not determined

Toxicity on invertebrates: not determined

Toxicity on invertebrates (Chronic toxicity): not determined

Bacteria toxicity (EC50): > 1,000 mg/l
Species: activated sludge
Method: OECD 209

12.2. Persistence and degradability

Irbesartan: Biological degradability: 22.5 %
Testing period: 28 d
The product is not readily biodegradable according to OECD criteria.
The product can be degraded by abiotic, e.g. chemical or photolytic, processes.
Although not readily biodegradable, the product is largely eliminated in sewage treatment plants.

Hydrochlorothiazide: < 20 %
Not readily degradable
Testing period: 28 day
Method of analysis: DOC decrease
Method: Zahn-Wellens Test

12.3. Bioaccumulative potential

Unlikely to be bioaccumulative in living organisms (Log Kow < 3).

12.4 Mobility in soil

No data available.

12.5 Other adverse effects

Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

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13. Disposal Considerations

13.1 Disposal of product waste

Disposal should be in accordance with applicable regional, national and local laws and regulations. Local regulations may be more stringent than regional or national requirements.

13.2 Disposal of packaging waste

Dispose of in a safe manner in accordance with federal, state and local environmental regulations. Empty packages, containers or liners may contain product residue.

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14. Transport Information

14.1 Basic shipping information, finished product

U.S. DOT	Not a regulated material.
ICAO/IATA	Not a regulated material.
IMDG	Not a regulated material.

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15. Regulatory Information

US Regulations
CERCLA Hazardous Substance List (40 CFR 302.4): Not listed.
Clean Water Act Section 311 Hazardous Substances (40 CFR 117.3): Not listed.
Clean Air Act (CAA) Section 112(r) Accidental Release Prevention (40 CFR 68.130): Not listed.
SARA Title III:
Section 302 Extremely Hazardous Substance (40 CFR 355, Appendix A): Not listed.
Section 313 Toxic Release Inventory (40 CFR 372): Not listed.

State Regulations
California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65): Titanium dioxide (airborne, unbound particles of respirable size).
Massachusetts Right-To-Know List: Titanium dioxide.
New Jersey Right-To-Know List: Titanium dioxide.
Pennsylvania Right-To-Know List: Titanium dioxide.

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16. Other Information

Other Information: The information contained herein is based upon data considered true and accurate. Sanofi-aventis U.S. LLC. makes no warranties, express or implied, as to the adequacy of the information contained herein. This information is offered solely for the user's consideration, investigation and verification. Report to the manufacturer any allegations of health effects resulting from handling or accidental contact with this material.

Abbreviations and Acronyms
CAS: Chemical Abstracts Service
DOT: U.S. Department of Transportation
EST: Eastern standard time (U.S.)
IATA: International Air Transport Association
IMDG: International Maritime Dangerous Goods Code
LC50: Lethal concentration, 50%
LD50: Lethal dose, 50%
OEL: Occupational Exposure Limit
PPE: Personal Protection Equipment
SDS: Safety Data Sheet
STEL: Short-term exposure limit
TWA: Time-weighted average
U.S.: United States

Date Prepared : November 16, 2016

Second version.