1 NAME OF THE MEDICINE

Irbesartan/hydrochlorothiazide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Irbesartan HCT Winthrop 150/12.5 tablets contain 150mg of irbesartan and 12.5mg of hydrochlorothiazide.

Irbesartan HCT Winthrop 300/12.5 tablets contain 300mg of irbesartan and 12.5mg of hydrochlorothiazide.

Irbesartan HCT Winthrop 300/25 tablets contain 300mg of irbesartan and 25mg of hydrochlorothiazide.

Irbesartan is a white to off-white crystalline powder. It is a relatively non-polar compound with a partition coefficient (octanol-water) of 10.1 at a pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride, and practically insoluble in water.

Hydrochlorothiazide is a white crystalline powder. It is slightly soluble in water but freely soluble in sodium hydroxide solution.

Excipients of known effect: lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Irbesartan HCT Winthrop 150/12.5 tablets are peach to mottled peach coloured, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2875” on the other side.

Irbesartan HCT Winthrop 300/12.5 tablets are peach to mottled peach coloured, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2876” on the other side.

Irbesartan HCT Winthrop 300/25 tablets are pink, biconvex, oval-shaped, film-coated tablets debossed with a heart on one side and the number “2788” on the other side.
4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Irbesartan HCT Winthrop is indicated for the treatment of hypertension. Treatment should not be initiated with this fixed-dose combination.

4.2 DOSE AND METHOD OF ADMINISTRATION

Irbesartan HCT Winthrop should not be initiated as first-line therapy. The daily dose can be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect

When clinically appropriate, direct change from monotherapy to the fixed combinations may be considered:

- Irbesartan HCT Winthrop 150/12.5 mg may be administered to patients whose blood pressure is not adequately controlled with hydrochlorothiazide or irbesartan 150 mg alone.
- Irbesartan HCT Winthrop 300/12.5 mg may be administered to patients insufficiently controlled by irbesartan 300 mg or by Irbesartan HCT Winthrop 150/12.5 mg.
- Irbesartan HCT Winthrop 300/25 mg may be administered to patients insufficiently controlled by Irbesartan HCT Winthrop 300/12.5 mg.

Doses higher than 300 mg irbesartan/25 mg hydrochlorothiazide once daily are not recommended. When necessary, Irbesartan HCT Winthrop may be administered with another antihypertensive drug.

Patients with Intravascular Volume Depletion

In severely volume-depleted and/or sodium-depleted patients, such as those treated vigorously with diuretics, the condition should be corrected prior to administration of Irbesartan HCT Sanofi.

Elderly Patients

No dosage reduction is generally necessary for daily dosage of irbesartan 150mg/hydrochlorothiazide 12.5mg in the elderly.

Patients with Renal Impairment

No dosage reduction is generally necessary for daily dosage of irbesartan 150mg/hydrochlorothiazide 12.5mg in patients with mild-to-moderate renal impairment (creatinine clearance >30mL/min).
**Patients with Hepatic Impairment**

No dosage reduction is thought to be necessary in patients with mild to moderate hepatic impairment as the pharmacokinetics of neither irbesartan nor hydrochlorothiazide are affected by hepatic impairment. Due to the hydrochlorothiazide component, Irbesartan HCT Winthrop should be used with caution in patients with severe hepatic impairment (See Section 4.4 Special warnings and precautions for use).

### 4.3 CONTRAINDICATIONS

- Irbesartan HCT Winthrop is contraindicated in patients who are hypersensitive to irbesartan, sulphonamide derived drugs (e.g. thiazides), or to any other component of the Irbesartan HCT Winthrop formulation. In general, hypersensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

- Irbesartan HCT Winthrop is contraindicated in patients who are anuric.

- Do not co-administer Irbesartan HCT Winthrop with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment.

- Do not co-administer Irbesartan HCT Winthrop with ACE inhibitors in patients with diabetic nephropathy.

- Pregnancy. (See Section 4.6 Fertility, pregnancy and lactation)

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Hypotension - Volume - Depleted Patients**

Irbesartan HCT Winthrop has been rarely associated with hypotension in hypertensive patients without other risk factors for hypotension. Symptomatic hypotension may be expected to occur in patients who have been sodium and/or volume depleted by vigorous diuretic therapy and/or dietary salt restriction, or vomiting and/or diarrhoea or haemodialysis. Volume and/or sodium-depletion should be corrected before initiating therapy with Irbesartan HCT Sanofi. Thiazides may potentiate the action of other antihypertensive drugs (see Section 4.5 Interactions with other medicines and other forms of interactions).

**Renal Impairment**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function during therapy with Irbesartan HCT Winthrop may be anticipated in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g. hypertensive patients with renal artery stenosis in one or both kidneys, or patients with severe congestive heart failure), treatment with drugs that affect this system has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. The possibility of a similar effect occurring with the use of an angiotensin II receptor antagonist, including Irbesartan HCT Sanofi, cannot be excluded.

There is no experience with Irbesartan HCT Winthrop in patients with a recent renal transplant.
Irbesartan HCT Winthrop is not recommended for patients with severe renal disease (creatinine clearance ≤30 mL/min) (see Section 4.3 Contraindications). Hydrochlorothiazide-associated precipitation of azotemia may occur in patients with impaired renal function. As experience is limited in patients with a creatinine clearance >30 and <60mL/min, Irbesartan HCT Winthrop should be administered with caution to such patients.

**Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS)**

Dual blockade of the RAAS by combining Irbesartan HCT Winthrop with an ACE inhibitor or with aliskiren is not recommended since there are increased risks of hypotension, hyperkalemia, and changes in renal function. The use of Irbesartan HCT Winthrop in combination with aliskiren is contraindicated in patient with diabetes mellitus or renal impairment (see Section 4.3 Contraindications).

The use of Irbesartan HCT Winthrop in combination with aliskiren is contraindicated in patients with diabetes mellitus or with moderate to severe renal impairment.

The use of Irbesartan HCT Winthrop in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (See Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

The use of Irbesartan HCT Winthrop in patients with psoriasis or a history of psoriasis should be carefully weighed as it may exacerbate psoriasis.

**Renal Artery Stenosis**

See comments under Renal Impairment, above.

**Primary Aldosteronism**

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore the use of Irbesartan HCT Winthrop is not recommended.

**Postsympathectomy**

The antihypertensive effects of thiazide diuretics may be increased in the postsympathectomy patient.

**Fluid and Electrolyte Imbalance**

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Although hypokalaemia may develop when thiazide diuretics are used alone, especially with higher doses, concurrent therapy with irbesartan reduces the frequency of diuretic-induced hypokalaemia. Chloride deficit is generally mild and usually does not require treatment. Calcium excretion is decreased by thiazides which may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia suggests the possibility of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
Monitoring of laboratory parameters may be necessary in patients at risk of electrolyte imbalance.

**Metabolic and Endocrine Effects**

Hyperuricaemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy. Insulin requirements in diabetic patients may be increased and latent diabetes mellitus may become manifest during thiazide administration. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy, however, minimal or no effects were reported at the 12.5 mg hydrochlorothiazide dose contained in Irbesartan HCT Sanofi.

Monitoring of laboratory parameters may be necessary in patients at risk of metabolic disturbances.

**Systemic Lupus Erythematosus**

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

**Secondary Acute Angle-Closure Glaucoma and/or Acute Myopia**

Hydrochlorothiazide is a sulfonamide. Sulfonamide, or sulfonamide derivative, drugs can cause an idiosyncratic reaction, which may result in secondary acute angle-closure glaucoma and/or acute myopia. Isolated cases of acute angle-closure glaucoma without definite causal association have been reported with hydrochlorothiazide. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy (see Section 4.8 Adverse effects(undesirable effects)).

**Heart Failure**

The safety of irbesartan in the presence of heart failure has not been fully defined. Sudden death has occurred in some studies of patients with heart failure, and although such deaths may have reflected the natural history of the underlying heart failure, caution is recommended when treating such patients with irbesartan.

**Cardiac Arrhythmia**

At this time, experience is limited with irbesartan in the treatment of patients with ventricular dysfunction or cardiac arrhythmias; caution is advised.

**Use in Hepatic Impairment**

Irbesartan HCT Winthrop should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations in fluid and electrolyte balance may precipitate hepatic coma.
Use in Renal Impairment

See comments under Renal Impairment, above.

Use in the Elderly

Among patients who received Irbesartan HCT Winthrop in clinical studies, no overall differences in efficacy or safety were observed between older patients (65 years or older) and younger patients.

Paediatric Use

Safety and effectiveness in paediatric patients have not been established.

Effects on Laboratory Tests

In premarketing controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Irbesartan HCT Winthrop tablets.

Creatinine, Blood Urea Nitrogen

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3 and 1.1 percent, respectively, of patients with essential hypertension treated with Irbesartan HCT Winthrop alone. No patient discontinued taking Irbesartan HCT Winthrop due to increased BUN. One patient discontinued taking Irbesartan HCT Winthrop due to a minor increase in creatinine.

Haemoglobin

Mean decreases of approximately 0.2 g/dL occurred in patients treated with Irbesartan HCT Winthrop alone, but were rarely of clinical importance. This compared to a mean of 0.4 g/dL in patients receiving placebo. No patients were discontinued due to anaemia.

Liver Function Tests

Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Irbesartan HCT Winthrop alone, one patient was discontinued due to elevated liver enzymes.

Serum Electrolytes

In double-blind clinical trials of various doses of irbesartan and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalaemia (serum potassium <3.5 mmol/L) was 7.5% versus 6.0% for placebo; the incidence of hyperkalaemia (serum potassium >5.7 mmol/L) was <1.0% versus 1.7% for placebo. No patient discontinued due to increases or decreases in serum potassium. Overall, the combination of irbesartan and hydrochlorothiazide had no effect on serum potassium. Higher doses of irbesartan ameliorated the hypokalaemic response to hydrochlorothiazide (See Section 4.4 Special warnings and precautions for use).
4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Based on in vitro data, no interactions with irbesartan would be expected to occur with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 or CYP3A4. Irbesartan is primarily metabolized by CYP2C9, however, during clinical interaction studies, no significant pharmacokinetic and pharmacodynamic interactions were observed when irbesartan was co-administered with warfarin (a drug metabolized by CYP2C9).

Irbesartan does not affect the pharmacokinetics of digoxin or simvastatin. The pharmacokinetics of irbesartan are not affected by coadministration with nifedipine or hydrochlorothiazide.

Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase kalaemia with irbesartan may lead to increases in serum potassium, sometimes severe, and requires close monitoring of serum potassium. Concurrent therapy with hydrochlorothiazide may reduce the frequency of this effect.

**Alcohol, barbiturates or narcotics**

Potentiation of thiazide diuretic-induced orthostatic hypotension may occur.

**Antidiabetic drugs (oral agents and insulin)**

Thiazides may elevate blood glucose levels thus dosage adjustments of antidiabetic agents may be necessary.

**Antigout medication**

Dosage adjustments of antigout medication may be needed since hydrochlorothiazide may raise the blood level of uric acid.

**Cardiac glycosides (e.g. digoxin) and other antiarrhythmic drugs (e.g. sotalol)**

Diuretic-induced hypokalaemia may accentuate cardiac arrhythmias.

**Calcium salts**

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium or a calcium sparing drug (e.g. Vitamin D therapy) is prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

**Cholestyramine resin and colestipol HCl**

May delay or decrease absorption of hydrochlorothiazide. Irbesartan HCT Winthrop should be taken at least one hour before, or four hours after these medications.
Lithium

Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of irbesartan. Co-administration with Irbesartan HCT Winthrop should be approached with caution and frequent monitoring of serum lithium levels is recommended.

Inhibitors of Endogenous Prostaglandin Synthesis (i.e. NSAIDs)

In some patients, these agents can reduce the effects of thiazide diuretics.

Other diuretics and antihypertensive medications

The thiazide component of Irbesartan HCT Winthrop may potentiate the actions of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. Hydrochlorothiazide may interact with diazoxide; blood glucose, serum uric acid levels and blood pressure should be monitored.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID, including COX-2 inhibitor) alone or with a thiazide diuretic may increase the risk of renal impairment, including possible acute renal failure. These effects are usually reversible. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly, volume-depleted and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter. The antihypertensive effect of angiotensin II receptor antagonists, including irbesartan, may be attenuated by NSAIDs including selective COX-2 inhibitors.

The use of Irbesartan HCT Winthrop in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy (See Section 4.3 Contraindications and Section 4.5 Interactions with other medicines and other forms of interactions).

Renin inhibitor

The combination of Irbesartan HCT Winthrop with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or moderate to severe renal impairment and is not recommended in other patients (see Section 4.3 Contraindications).

Angiotensin-Converting Enzyme inhibitors (ACE inhibitors)

The use of Irbesartan HCT Winthrop in combination with an ACE inhibitor is contraindicated in patients with diabetic nephropathy and is not recommended in other patients.

Drugs used during surgery

The effects of nondepolarising muscle relaxants (e.g. tubocurarine), preanaesthetics and anaesthetics used in surgery may be potentiated by hydrochlorothiazide; dosage adjustments
may be required. Preanaesthetic and anaesthetic agents should be given in reduced dosage, and if possible, hydrochlorothiazide therapy discontinued one week prior to surgery.

**Carbamazepine**

Concomitant use of carbamazepine and hydrochlorothiazide has been associated with the risk of symptomatic hyponatraemia. Electrolytes should be monitored during concomitant use. If possible, another class of diuretics should be used.

**Pressor amines (e.g. noradrenaline)**

Due to the thiazide component there is a possible decreased response to pressor amines but not sufficient to preclude their use.

**Corticosteroids, ACTH**

Intensified electrolyte depletion, particularly hypokalaemia can occur with thiazide use.

**Other interactions**

The hypoglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

**4.6 FERTILITY, PREGNANCY AND LACTATION**

**Effects on Fertility**

The effects of hydrochlorothiazide and the irbesartan/hydrochlorothiazide combination on fertility have not been evaluated in animal studies. However, with irbesartan alone, fertility and reproductive performance were not affected in studies of male and female rats at oral doses up to 650mg/kg/day (approximately 3 [male] and 8[female] fold higher exposure based on AUC, than that of humans at the maximum recommended clinical dose of 300mg/day.)

**Use in Pregnancy**

Category D

Drugs that act directly on the renin-angiotensin system can cause foetal 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, Irbesartan HCT Winthrop 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 have been associated with foetal 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 foetal
renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation 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 whose embryos and foetuses are exposed 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 Irbesartan HCT Winthrop as soon as possible.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard, including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

No teratogenic effects were seen in rats given irbesartan and hydrochlorothiazide in combination at doses as high as 150/150 mg/kg/day. When pregnant rats were treated with irbesartan alone from day 0 to day 20 of gestation, at doses of 50 mg/kg/day and higher, transient effects (increased renal pelvic cavitation, hydroureret or subcutaneous oedema) were noted in full term rat foetuses but not in young animals necropsied after six weeks of age. In pregnant rabbits, at doses of 30 mg/kg/day, maternal mortality, abortion and early foetal resorptions were noted. No teratogenic effects were observed in the rat or the rabbit.

Use in Lactation

Irbesartan is excreted in the milk of lactating rats. It is not known whether irbesartan or its metabolites are excreted in human milk. Hydrochlorothiazide is excreted in human breast milk. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of Irbesartan HCT Winthrop during breastfeeding is not recommended.

Because of the potential risk to the infant, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of Irbesartan HCT Winthrop to the therapy of the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of Irbesartan HCT Winthrop on the ability to drive motor vehicles or operate machinery have not been specifically studied, but based on its pharmacodynamic properties, Irbesartan HCT Winthrop is unlikely to affect this ability. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness may occur during treatment of hypertension.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The combination of irbesartan and hydrochlorothiazide has been evaluated for safety in approximately 2750 subjects in clinical studies, including 1540 hypertensive patients treated for over 6 months and over 960 patients treated for one year or more. Adverse events in patients
receiving Irbesartan HCT Winthrop were generally mild and transient with no relationship to dose. The incidence of adverse events was not related to age, gender, or race.

In placebo-controlled clinical studies, including 898 irbesartan/HCTZ-treated patients (usual duration of treatment 2 to 3 months), discontinuations due to any clinical or laboratory adverse event were 3.6 percent for irbesartan/HCTZ-treated patients and 6.8 percent for placebo-treated patients (p=0.023).

Adverse events occurring in at least 1% of patients treated with irbesartan/HCTZ, in placebo controlled trials are shown in the table below.

The incidences of the same adverse events in the placebo, irbesartan and hydrochlorothiazide control groups are also shown.

### Table 1 - Adverse Events in Placebo-Controlled Hypertension Trials

<table>
<thead>
<tr>
<th>BODY SYSTEM/EVENT</th>
<th>Incidence Percentage (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irbesartan/HCTZ n=898</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>1.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.5 *</td>
</tr>
<tr>
<td>Influenza</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>3.1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.7</td>
</tr>
<tr>
<td>Anorectal disorder</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2.1</td>
</tr>
<tr>
<td>Dyspepsia/heartburn</td>
<td>2.1</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3.2 *</td>
</tr>
<tr>
<td><strong>Immunology/Sensitivity disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>1.1</td>
</tr>
<tr>
<td><strong>Musculoskeletal/Connective Tissue</strong></td>
<td></td>
</tr>
<tr>
<td>Musc/skeletal pain</td>
<td>6.5</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculoskeletal trauma</td>
<td>1.3</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Percentage (%) of Patients</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Anxiety/nervousness</td>
<td>1.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.6</td>
</tr>
<tr>
<td>Dizziness orthostatic</td>
<td>1.1</td>
</tr>
<tr>
<td>Headache</td>
<td>11.0 *</td>
</tr>
<tr>
<td></td>
<td>9.3 *</td>
</tr>
<tr>
<td></td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>16.1</td>
</tr>
<tr>
<td>Renal/Genitourinary</td>
<td></td>
</tr>
<tr>
<td>Abnormal urination</td>
<td>1.9</td>
</tr>
<tr>
<td>UTI</td>
<td>1.6</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>2.2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.1</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1.9</td>
</tr>
<tr>
<td>Sinus abnormality</td>
<td>2.9</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* Statistically significant difference compared with placebo, p<0.05

Adverse reactions (clinical events probably or possibly related to therapy as determined by the clinical investigator) that occurred in more than 2 hypertensive patients when they were taking irbesartan/hydrochlorothiazide and no additional study medications in premarketing clinical trials involving 2700 subjects, and that were not reported in the above tabulation of adverse events, are listed in the following section. These adverse reactions have been classified using standard terminology and are categorized by body system. They are listed in order of decreasing frequency according to the following definitions:

common: those adverse reactions occurring on one or more occasions in at least 1/100 but less than 1/10 patients;

uncommon: adverse reactions occurring in at least 1/1000 but less than 1/100 patients;

rare: those adverse reactions occurring in less than 1/1000 patients.

**Cardiovascular**

Uncommon - bradycardia; disturbance of cardiac rhythm; subjective disturbance of cardiac rhythm; disturbance of ventricular rhythm; ECG abnormality; flushing; hypotension; orthostatic hypotension; syncope.

**Dermatologic**

Uncommon - pruritus; skin discomfort.
**Endocrine/Metabolic**

Common - sexual dysfunction;

Uncommon - diabetes; gout; hot flashes; libido changes.

**Gastrointestinal**

Uncommon - constipation; decreased appetite; abdominal distention; dry mouth; epigastric pain; flatulence; gastroesophageal reflux.

**General**

Uncommon - cold sensation; hyperhidrosis; malaise; weakness; weight gain.

**Musculoskeletal/Connective Tissue**

Uncommon - abnormal reflexes; muscle ache; myalgia; extremity swelling; extremity weakness.

**Nervous System**

Uncommon - coordination disturbance; depression; emotional lability/disturbance; numbness; paraesthesia; sleep disturbance; somnolence; vertigo.

**Respiratory**

Uncommon - dry nasopharynx; dyspnoea; wheezing.

**Special Senses**

Uncommon - abnormal hearing; taste disturbance; vision disturbance.

**Other clinical adverse reactions reported with the use of irbesartan or hydrochlorothiazide alone include:**

**Cardiovascular**

Subjective rhythm disturbance, flushing, ECG abnormality, cardiac murmur, cardiac rhythm disturbance, orthostatic hypotension, atrial rhythm disturbance, conduction disorder, myocardial infarction.

**Dermatologic**

Facial erythema, dermatitis, acne, scalp-hair abnormality.

**Endocrine/Metabolic/Electrolyte Imbalance**

Breast disorder, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia).
**Gastrointestinal**
Abnormal stool, increased appetite, oral lesion, dysphagia, oesophagitis, anorexia, gastric irritation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis, xanthopsia.

**General**
Weakness, weight gain, warmth sensation, pain.

**Haematopoietic**
Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, anaemia, aplastic anaemia, haemolytic anaemia.

**Immunology/Sensitivity Disorder**
Upper extremity oedema, head/neck oedema, photosensitivity reactions, fever, urticaria, necrotizing angiitis, (vasculitis, cutaneous vasculitis), respiratory distress (including pneumonitis and pulmonary oedema), anaphylactic reactions, toxic epidermal necrolysis.

**Musculoskeletal/Connective Tissue**
Arthritis, stiffness lower extremity, muscle spasm, weakness.

**Nervous System**
Stress related disorder, tremor, disturbing dreams, restlessness.

**Renal/Genitourinary**
Urination abnormality, renal dysfunction, interstitial nephritis.

**Respiratory**
Epistaxis.

**Special Senses**
Eye disturbance-other, eyelid abnormality, visual field abnormality, medication bad taste, eye disorders (transient blurred vision, secondary acute angle-closure glaucoma and/or acute myopia) (see Section 4.4 Special warnings and precautions for use).

**Post-marketing experience**
As with other angiotensin-II receptor antagonists, hypersensitivity reactions (urticaria, angioedema, anaphylactic reactions including anaphylactic shock) have been reported. The following have been reported during post marketing surveillance: vertigo, arthralgia, asthenia, hyperkalaemia, thrombocytopenia (including thrombocytopenic purpura), myalgia, tinnitus, jaundice, elevated liver function tests, hepatitis, psoriasis (and psoriasis exacerbation) (see Section 4.4 Special warnings and precautions for use), photosensitivity and impaired renal function including cases of renal failure in patients at risk.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

**Reporting suspected adverse effects**

Reporting of suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

### 4.9 OVERDOSE

Experience in adults exposed to irbesartan doses of up to 900 mg/day for 8 weeks revealed no toxicity. No specific information is available on the treatment of overdosage with Irbesartan HCT Sanofi. The patient should be closely monitored, and the treatment should be symptomatic and supportive, including fluid and electrolyte replacement. Irbesartan is not removed from the body by haemodialysis.

The most common signs and symptoms observed in adults exposed to hydrochlorothiazide are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If a cardiac glycoside (e.g. digoxin) or other antiarrhythmic drugs (e.g. sotalol) has also been administered, hypokalaemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

For information on the management of overdose, contact the Poisons Information Centre, on 131126 (Australia).

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: angiotensin II antagonists and diuretics, ATC code: C09DA04.

**Mechanism of Action**

Irbesartan is a specific antagonist of angiotensin II receptors (AT$_1$ subtype). Angiotensin II is an important component of the renin-angiotensin system and is involved in the pathophysiology of hypertension and in sodium homeostasis. Irbesartan does not require metabolic activation for its activity.

Irbesartan blocks the potent vasoconstrictor and aldosterone-secreting effects of angiotensin II by selective antagonism of the angiotensin II (AT$_1$ subtype) receptors localized on vascular smooth muscle cells and in the adrenal cortex. It has no agonist activity at the AT$_1$ receptor and a much greater affinity (more than 8500-fold) for the AT$_1$ receptor than for the AT$_2$ receptor (a receptor that has not been shown to be associated with cardiovascular homeostasis).
Irbesartan does not inhibit enzymes involved in the renin-angiotensin system (i.e., renin, angiotensin converting enzyme [ACE]) or affect other hormone receptors or ion channels involved in the cardiovascular regulation of blood pressure and sodium homeostasis.

Hydrochlorothiazide is a benzothiadizine (thiazide) diuretic with diuretic, natriuretic and antihypertensive effects. The mechanism of antihypertensive effect of thiazide diuretics, such as hydrochlorothiazide is not fully known. Thiazides affect the renal tubular mechanism of electrolyte reabsorption, increasing excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate. Hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

Clinical Trials

Based on data from placebo-controlled clinical trials, the following effects were noted. The blood pressure lowering effect of irbesartan in combination with hydrochlorothiazide was apparent after the first dose and substantially present within 1-2 weeks, with the maximal effect occurring by 6-8 weeks. In long-term follow-up studies, the blood pressure lowering effect of irbesartan/hydrochlorothiazide with dose-to-response addition of adjunctive therapy was maintained for over one year.

The combination of hydrochlorothiazide and irbesartan produced dose-related additive reductions in blood pressure across their therapeutic dose ranges. The addition of 12.5 mg hydrochlorothiazide to 300 mg irbesartan once daily in patients not adequately controlled on 300 mg irbesartan alone resulted in further placebo-corrected diastolic blood pressure reductions at trough (24 hours post dosing) of 6.1 mmHg. The combination of 300 mg irbesartan and 12.5 mg hydrochlorothiazide resulted in an overall placebo-subtracted systolic/diastolic reduction of up to 13.6/11.5 mmHg.

Limited clinical data (7 out of 22 patients) suggest that patients not controlled with 300/12.5 mg combination may respond when uptitrated to 300/25 mg. In these patients, an incremental blood pressure lowering effect was observed for both SBP and DBP (13.3 and 8.3 mmHg, respectively).

Once daily dosing with 150 mg irbesartan and 12.5 mg hydrochlorothiazide showed systolic/diastolic mean placebo-adjusted blood pressure reductions at trough (24 hours post-dosing) of 12.9/6.9mmHg. Peak effects occurred at 3-6 hours.

When assessed by ambulatory blood pressure monitoring, Irbesartan HCT Winthrop 150/12.5 once daily produced consistent reduction in blood pressure over the 24 hours period with a mean 24-hour placebo-subtracted systolic/diastolic reductions of 15.8/10.0 mmHg. The observed trough-to-peak effects were at least 68% of the corresponding placebo-subtracted peak diastolic and peak systolic responses.

In a clinical trial with patients not adequately controlled on 25 mg hydrochlorothiazide alone after 4 weeks’ treatment, the addition of irbesartan (with dose-to-response uptitration from 75 mg to 150 mg at 6 weeks) produced mean systolic/diastolic reductions at 12 weeks which were 11.1/7.2 mmHg greater than hydrochlorothiazide alone.

Blood pressure was lowered to about the same extent in both standing and supine positions. Orthostatic effects were infrequent, but may be expected to occur in patients who develop intercurrent sodium and/or volume-depletion.
The effect of the combination of irbesartan and hydrochlorothiazide on morbidity and mortality has not been studied. Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effectiveness of irbesartan/hydrochlorothiazide was not influenced by age, race, or gender. The overall antihypertensive response to the combination was similar for black and non black patients.

After withdrawal of irbesartan, blood pressure gradually returned toward baseline. Rebound hypertension was not observed with irbesartan or hydrochlorothiazide.

With hydrochlorothiazide, onset of diuresis occurred in 2 hours, and peak effect occurred at about 4 hours, while the action persisted for approximately 6-12 hours.

5.2 PHARMACOKINETIC PROPERTIES

Concomitant administration of hydrochlorothiazide and irbesartan has no effect on the pharmacokinetics of either drug

Absorption

The oral bioavailabilities of irbesartan and hydrochlorothiazide measured after administration of Irbesartan HCT Winthrop are similar to the bioavailabilities of irbesartan and hydrochlorothiazide administered as separate entities. The absolute oral bioavailability for irbesartan has previously been shown to be 60-80% whilst the absolute oral bioavailability for hydrochlorothiazide is documented as 50-80%.

Food does not affect the bioavailability of Irbesartan HCT Sanofi. Peak plasma concentrations occur 1.5-2 hours after oral administration for irbesartan and 1-2.5 hours for hydrochlorothiazide.

Distribution

Irbesartan is 90% protein-bound in the plasma, and has negligible binding to cellular components of blood. The volume of distribution is 53-93 litres (0.72-1.24 L/kg). Hydrochlorothiazide is 68% protein-bound in the plasma, and its apparent volume of distribution is 0.83-1.141 L/kg.

Metabolism

In plasma, unchanged irbesartan accounts for more than 80% of the circulating radioactivity following oral or intravenous administration of 14C irbesartan. Irbesartan is metabolized by the liver via glucuronide conjugation and oxidation. The major circulating metabolite is irbesartan glucuronide (~6%). Irbesartan undergoes oxidation primarily by the cytochrome P450 isoenzyme CYP2C9; isoenzyme CYP3A4 has negligible effect. It is not metabolized by, nor does it substantially induce or inhibit most isoenzymes commonly associated with drug metabolism (i.e. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2D6, or CYP2E1). Irbesartan does not induce nor inhibit isoenzyme CYP3A4.

Hydrochlorothiazide is not metabolized.
Excretion

Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20% of the administered radioactivity after an oral or intravenous dose of $^{14}$C irbesartan is recovered in urine with the remainder in the faeces. Less than 2% of the dose is excreted in urine as unchanged irbesartan.

The terminal elimination half-life ($t_{1/2}$) of irbesartan from plasma is 11-15 hours. The total body clearance of intravenously administered irbesartan is 157-176 mL/min, of which 3.0-3.5mL/min is renal clearance. Irbesartan exhibits linear pharmacokinetics over the therapeutic dose range. Steady-state plasma concentrations are attained within 3 days after initiation of a once-daily dosing regimen. Limited accumulation (<20%) is observed in plasma upon repeated once-daily dosing.

Hydrochlorothiazide is eliminated by the kidneys. The mean plasma half-life ($t_{1/2}$) of hydrochlorothiazide from plasma reportedly ranges from 5-15 hours.

Special Populations

In male and female hypertensive subjects, higher (11-44%) plasma concentrations of irbesartan were observed in females than in males, although, following multiple dosing, males and females did not show differences in either accumulation or elimination half-life. No gender-specific differences in clinical effect have been observed.

In elderly (male and female) normotensive subjects (65-80 years) with clinically normal renal and hepatic function, the plasma AUC and peak plasma concentration ($C_{max}$) of irbesartan are approximately 20%-50% greater than those observed in younger subjects (18-40 years). Regardless of age, the elimination half-life is comparable. No significant age-related differences in clinical effect have been observed. The area under the plasma concentration time curve (AUC) for hydrochlorothiazide was elevated in the elderly group following multiple dosing consistent with previously published data.

In black and white normotensive subjects, the plasma AUC and $t_{1/2}$ of irbesartan are approximately 20-25% greater in blacks than in whites; the peak plasma concentrations ($C_{max}$) of irbesartan are essentially equivalent.

In patients with renal impairment (regardless of degree) and in haemodialysis patients, the pharmacokinetics of irbesartan are not significantly altered. Irbesartan is not removed by haemodialysis. In patients with severe renal impairment (creatinine clearance <20 mL/min), the elimination half-life of hydrochlorothiazide was reported to increase to 21 hours.

In patients with hepatic insufficiency due to mild to moderate cirrhosis, the pharmacokinetics of irbesartan are not significantly altered.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Irbesartan and the irbesartan/hydrochlorothiazide combination were not genotoxic in a series of assays for gene-mutagenic activity in bacterial and mammalian cells, and for clastogenic effects in vitro and in vivo. Hydrochlorothiazide alone was not genotoxic in a gene-mutation assay in bacterial cells, or in tests for clastogenic activity in vitro and in vivo. However,
positive results were obtained in a mammalian cell assay for gene mutation (mouse lymphoma cell assay), and in two other tests (sister chromatid exchange assay in Chinese hamster ovary cells and non-disjunction assay in *Aspergillus nidulans*).

**Carcinogenicity**

The carcinogenic potential of irbesartan and hydrochlorothiazide in combination has not been evaluated in animal studies. However, the carcinogenic potential of irbesartan was assessed in two 104 week studies in mice and rats. No carcinogenic potential was observed in either species at doses of up to 500mg/kg/day (male rats) and 1000mg/kg/day (mice and female rats). The AUC based exposure levels were 3-6 fold higher in mice, 3 fold higher in male rats and 25 fold higher in female rats than that of humans at the maximum recommended clinical dose of 300mg/day. With hydrochlorothiazide two-year feeding studies in mice and rats uncovered no evidence of carcinogenic potential in female mice at doses up to approximately 600mg/kg/day, or in male and female rats at doses up to approximately 100mg/kg/day. The studies, however, uncovered equivocal evidence for hepatocarcinogenicity in male mice treated with hydrochlorothiazide at approximately 600mg/kg/day.

### 6  PHARMACEUTICAL PARTICULARS

#### 6.1  LIST OF EXCIPIENTS

The inactive ingredients in *Irbesartan HCT Winthrop* 150/12.5 & 300/12.5 tablets include: carnauba wax, croscarmellose sodium, hypromellose, iron oxide red CI 77491, iron oxide yellow CI 77492, lactose, macrogol 3000, magnesium stearate, microcrystalline cellulose, silicon dioxide, and titanium dioxide.

The inactive ingredients in *Irbesartan HCT Winthrop* 300/25 tablets include: carnauba wax, croscarmellose sodium, hypromellose, iron oxide black CI 77499, iron oxide red CI 77491, iron oxide yellow CI 77492, lactose, macrogol 3350, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, silicon dioxide, and titanium dioxide.

#### 6.2  INCOMPATIBILITIES

Incompatibilities were either not accessed or not identified as part of the registration of this medicine.

#### 6.3  SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

#### 6.4  SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C
6.5 NATURE AND CONTENTS OF CONTAINER

Pack sizes include: 3*, 5*, 7*, 14*, 28*, 30*, 56* and 98* tablets in polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVDC/Al) blisters.

* presentations currently not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Irbesartan: 2-butyl-3-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4,4]non-1-en-4-one.

Hydrochlorothiazide: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Chemical Structure

The chemical structure of irbesartan is

![Chemical structure of irbesartan](image)

The empiric formula is C_{25}H_{28}N_{6}O and the molecular weight, 428.5.

The chemical structure of hydrochlorothiazide is:

![Chemical structure of hydrochlorothiazide](image)

The empiric formula is C_{7}H_{6}ClN_{3}O_{4}S_{2} and the molecular weight, 297.7.

CAS Number

The CAS registry number for irbesartan is: CAS-138402-11-6.
The CAS registry number for hydrochlorothiazide is: CAS-58-93-5.
7  MEDICINE SCHEDULE

Schedule 4

8  SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW 2113
Australia
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

9  DATE OF FIRST APPROVAL

13 November 2012

10  DATE OF REVISION

19 April 2018

Irbesartan HCT Winthrop is a sanofi-aventis trademark.

<table>
<thead>
<tr>
<th>SUMMARY TABLE OF CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Section Changed</strong></td>
</tr>
<tr>
<td>All</td>
</tr>
<tr>
<td>4.4</td>
</tr>
<tr>
<td>4.8</td>
</tr>
<tr>
<td>5.1</td>
</tr>
</tbody>
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