# RESOLOR®

## 1. PRODUCT DESCRIPTION

RESOLOR®

### 1.1 Dosage Forms and Strengths

Film-coated tablets, each containing 1 mg prucalopride as prucalopride succinate. Film-coated tablets, each containing 2 mg prucalopride as prucalopride succinate.

For excipients, see List of Excipients.

## 2. INDICATIONS

RESOLOR® is indicated for symptomatic treatment of chronic constipation in adults in whom laxatives fail to provide adequate relief.

## 3. DOSAGE AND ADMINISTRATION

### 3.1 Dosage

*Adults*
2 mg once daily.

*Geriatric (> 65 years)*
Start with 1 mg once daily [*see Geriatric Patients (10.5)*]; if needed the dose can be increased to 2 mg once daily.

*Children and adolescents*
RESOLOR® is not recommended in children and adolescents younger than 18 years [*see Pediatric Patients (10.4), CLINICAL STUDIES (12)*].

*Patients with renal impairment*
The dose for patients with severe renal impairment (GFR < 30 ml/min/1.73 $m^2$) is 1 mg once daily [*see CONTRAINDICATIONS (4), Renal Impairment (10.7)*]. No dose adjustment is required for patients with mild to moderate renal impairment.

*Patients with hepatic impairment*
Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2mg if required to improve efficacy and if the 1mg dose is well tolerated (see Special Warnings and Special Precautions for Use and Pharmacokinetic Properties). No dose adjustment is required for patients with mild to moderate hepatic impairment.

In clinical trials, a doubling of the daily dose to 4 mg did not lead to an increase in efficacy.

If the intake of once daily RESOLOR® is not effective after 4 weeks of treatment, the patient should be re-examined and the benefit of continuing treatment reconsidered.

If treatment is continued longer than 3 months, the benefit should be reassessed at regular intervals.

### 3.2 Method of Administration

RESOLOR® film-coated tablets are for oral use and can be taken with or without food.

## 4. CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Renal impairment requiring dialysis.
- Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, ulcerative colitis and toxic megacolon/megarectum.

## 5. WARNINGS AND PRECAUTIONS

### 5.1 Patients with Renal Impairment

Renal excretion is the main route of elimination of prucalopride [*see Pharmacokinetics (11.2)*]. A dose of 1 mg is recommended in patients with severe renal impairment [*see Dosage (3.1)*].

### 5.2 Concomittant Disease

There is limited information in patients with severe and clinically unstable concomitant disease (e.g. liver, cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS and other endocrine disorders). Therefore, caution should be exercised when prescribing RESOLOR® to patients with these conditions.

### 5.3 Oral Contraceptives

In case of severe diarrhea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive).

### 5.4 Suicidal Ideation and Behavior

In clinical trials and postmarketing experience, cases of suicide, suicide attempts, and suicidal ideation have been reported. A causal association between treatment with RESOLOR® and an increased risk of suicidal ideation and behavior has not been established.

Monitor all patients treated with RESOLOR® for persistent worsening of depression or the emergence of suicidal thoughts and behaviors. Counsel patients, their caregivers, and family members of patients to be aware of any unusual changes in mood or behavior and alert the healthcare provider immediately.

## 6. INTERACTIONS

Prucalopride has a low pharmacokinetic interaction potential. It is extensively excreted unchanged in urine (approximately 60% of the dose) via both passive filtration and active renal transporters (P-gp and BCRP) and *in vitro* metabolism is very slow. Although 7 different metabolites are known, the most abundant of these in plasma, R107504 (formed by O-demethylation and oxidation of the resulting alcohol function to a carboxylic acid) represents 0 – 1.7% of the plasma total radioactivity $AUC_{0\text{-}24}$.

Prucalopride did not inhibit specific CYP450 activities in *in vitro* studies in human liver microsomes at therapeutically relevant concentrations.

Prucalopride is a weak substrate for P-glycoprotein (P-gp). Prucalopride is a weak *in vitro* inhibitor of P-gp and BCRP transporters, and it is not a significant inhibitor of OATP1B3, OAT1, OAT3, BSEP and MRP2 transporters.

### 6.1 Effects of Prucalopride on Pharmacokinetics of Other Drugs

Prucalopride co-administration increased erythromycin $C_{max}$ by 40% and $AUC_{24h}$ by 28%. The mechanism for this interaction is not clear. The effect is not regarded as being clinically significant.

Prucalopride had no clinically relevant effects on the pharmacokinetics of warfarin, digoxin, alcohol, paroxetine or oral contraceptives.

### 6.2 Effects of Other Drugs on Pharmacokinetics of Prucalopride

Ketoconazole (200 mg twice/day), a potent inhibitor of CYP3A4 and of P-gp, increased the systemic exposure to prucalopride by approximately 40%. This effect is too small to be clinically relevant. Interactions of similar magnitude may be expected with other potent inhibitors of P-gp such as verapamil, cyclosporine A, and quinidine.

Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride.

### 6.3 Effect of Food

Interactions with food have not been observed.

### 6.4 Effects on Ability to Drive and Use Machines

RESOLOR® may have a minor influence on the ability to drive and use machines, since dizziness and fatigue have been observed in clinical studies, particularly during the first day of treatment (see Adverse Drug Reactions).

## 7. ADVERSE DRUG REACTIONS

In an integrated analysis of 17 double-blind placebo-controlled studies, RESOLOR® was given orally to approximately 3300 patients with chronic constipation. Of these patients over 1500 patients received RESOLOR® at the recommended dose of 2 mg per day, while about 1360 patients were treated with 4 mg RESOLOR® daily. The most frequently reported adverse reactions associated with RESOLOR® at the 2 mg daily dose are headache (17.8%) and gastrointestinal symptoms (abdominal pain (13.7%), nausea (13.7%) and diarrhea (12.0%)). The adverse reactions occur predominantly at the start of therapy and usually disappear within a few days with continued treatment. Other adverse reactions have been reported occasionally. The majority of adverse events were mild to moderate in intensity.

The following adverse reactions were reported in controlled clinical studies at the recommended dose of 2 mg with frequencies corresponding to *Very common* (≥ 1/10), *Common* (≥ 1/100 to < 1/10), and *Uncommon* (≥ 1/1000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are calculated based on the integrated analysis of 17 double-blind placebo-controlled clinical studies.

**Table 1. Adverse Drug Reactions (ADRs) Associated with RESOLOR®**

| System/ Organ Class | Adverse Drug Reaction |
|---|---|
| **Metabolism and nutrition disorders** | |
| Common: | decreased appetite |
| **Nervous system disorders** | |
| Very common: | headache |
| Common: | dizziness |
| Uncommon: | tremors, migraine |
| **Cardiac disorders** | |
| Uncommon: | palpitations |
| **Ear and labyrinth disorders** | |
| Uncommon: | vertigo |
| **Gastrointestinal disorders** | |
| Very common: | nausea, diarrhea, abdominal pain |
| Common: | vomiting, dyspepsia, flatulence, gastrointestinal sounds abnormal |
| Uncommon: | rectal hemorrhage |
| **Renal and urinary disorders** | |
| Uncommon: | pollakiuria |
| **General disorders and administration site conditions** | |
| Common: | fatigue |
| Uncommon: | pyrexia, malaise |

**Description of Selected Adverse Reactions**

Palpitations
Palpitations were reported in 0.7% of the placebo patients, 0.9% of the 1 mg RESOLOR® patients, 0.9% of the 2 mg RESOLOR® patients and 1.9% of the 4 mg RESOLOR® patients. The majority of patients continued using RESOLOR®. As with any new symptom, patients should discuss the new onset of palpitations with their physician.

Cardiovascular safety analysis
An evaluation was performed by an independent adjudication committee of all potential major adverse cardiovascular events (MACE) across 28 completed double-blind and open-label clinical studies for RESOLOR® in adult patients with chronic idiopathic constipation. The standardized incidence rate (IR) per 1000 subject-years for MACE for RESOLOR® was compared with the IR for placebo. The total exposure in the double-blind studies was 565.2 subject-years in the RESOLOR® group, 384 subject-years in the placebo group and 2769 subject-years in the double-blind and open-label clinical studies. The IR for MACE was 3.5 (2 subjects out of 3366) in the double-blind RESOLOR® group, 5.2 (2 subjects out of 2019) in the placebo group, and 3.3 (9 subjects out of 4472) for RESOLOR® in the combined double-blind and open-label clinical studies. The data do not indicate an increased risk of MACE attributable to RESOLOR® when compared to placebo.

Observational cardiovascular cohort study
The overall (CV) safety of RESOLOR® was assessed in an observational population-based cohort study using European healthcare databases. New users of RESOLOR® (N = 5715) were matched to new users of polyethylene glycol 3350 (PEG) (N = 29,372) to determine the standardized incidence rate (IR) and the adjusted incidence rate ratio (IRR) per 1,000 person-years for MACE. In this cohort study, the pooled, standardized IR for MACE was 6.57 (95% CI: 3.90, 10.39) for RESOLOR® compared to an IR of 10.24 (95% CI: 6.97, 14.13) for PEG and the IRR for MACE was 0.64 (95% CI: 0.36, 1.14). These data do not indicate an increased risk of MACE in patients using RESOLOR® as compared with patients using PEG for chronic idiopathic constipation.

## 8. OVERDOSE

In a study in healthy subjects, treatment with RESOLOR® was well-tolerated when given in an up-titrating scheme up to 20 mg once daily (10 times the recommended therapeutic dose). An overdose may result in symptoms resulting from an exaggeration of the medicinal product's known pharmacodynamic effects and include headache, nausea and diarrhea. Specific treatment is not available for RESOLOR® overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Extensive fluid loss by diarrhea or vomiting may require correction of electrolyte disturbances.

## 9. ABUSE AND DEPENDENCE

Not applicable.

## 10. SPECIAL POPULATIONS

### 10.1 Pregnancy

Experience with RESOLOR® during pregnancy is limited. Cases of spontaneous abortion have been observed during clinical studies, although, in the presence of other risk factors, the relationship to RESOLOR® is unknown. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development [*see NON-CLINICAL STUDIES (13)*].

RESOLOR® is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment with RESOLOR®.

### 10.2 Nursing Mothers

Prucalopride is excreted in breast milk. However, at therapeutic doses of RESOLOR® no effects on the breastfed newborns/infants are anticipated. In the absence of human data in women who breastfed while taking RESOLOR®, it is not recommended to use RESOLOR® during breast-feeding.

### 10.3 Fertility

Animal studies indicate that there is no effect on male or female fertility.

### 10.4 Pediatric patients

After a single oral dose of 0.03 mg/kg in pediatric patients aged 4 - 12 years, $C_{max}$ of prucalopride was comparable to the $C_{max}$ in adults after a single 2 mg dose. Unbound AUC was 30-40% lower than after 2 mg in adults. Unbound exposure was similar over the whole age-range (4-12 years). The average terminal half-life in pediatric patients was about 19 hours (range 11.6 to 26.8 hours). Safety and efficacy of prucalopride in pediatric patients was evaluated in a double-blind placebo controlled study. Efficacy results do not support the use of RESOLOR® in pediatric patients and therefore RESOLOR® is not recommended in this patient population [*see CLINICAL STUDIES (12)*].

### 10.5 Geriatric patients

After once daily dosing of 1 mg, peak plasma concentrations and AUC of prucalopride in geriatric patients were 26% - 28% higher than in young adults. This effect can be attributed to a diminished renal function in elderly.

### 10.6 Hepatic impairment

Non-renal elimination contributes up to about 35% of total elimination. After a single oral dose of 2 mg, $C_{max}$ and AUC of prucalopride were on average 10-20% higher in subjects with moderate and severe hepatic impairment than in subjects with normal hepatic function.

### 10.7 Renal impairment

Compared to subjects with normal renal function, plasma concentrations of prucalopride after a single 2 mg dose were on average 25% and 51% higher in subjects with mild ($Cl_{CR}$ 50-79 mL/min/1.73 $m^2$) and moderate ($Cl_{CR}$ 25-49 mL/min/1.73 $m^2$) renal impairment, respectively. In subjects with severe renal impairment ($Cl_{CR}$ ≤ 24 mL/min/1.73 $m^2$), plasma concentrations were 2.3 times the levels in healthy subjects [*see Dosage (3.1), WARNINGS AND PRECAUTIONS (5)*].

AMDIPHARM

| | |
|---|---|
| **AMS** Component No.: | **AW-LF-0001227 (v0.7)** |
| Product Description: | **RESOLOR 1MG 28 TABL. MALAYS., RESOLOR 2MG 28 TABL. MALAYS.** |
| Component: | Leaflet |
| Product Code: | 105278,105279 |
| Country: | Malaysia |
| Vendor Name: | Sanico NV |
| **Proof Number:** | **0.7** |
| Revision Date: | 09-Dec-2024 |
| Revised by: | PSC |

| | |
|---|---|
| Dimension: | 145 x 780 mm |
| Commodity No.: | N/A |
| Pharma Code: | N/A |
| Print Colours: | Black |
| Non-Print Colours: | Cutter |
| Min. Font Size: | 9 pt |

## 11. CLINICAL PHARMACOLOGY

### 11.1 Pharmacodynamics

Pharmacotherapeutic group: Other drugs for constipation
ATC code: A06AX05.

11.1.1 Mechanism of actions

Prucalopride, a high affinity selective, serotonin type 4 (5-$HT_4$) receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis increasing bowel motility. This peristalsis is referred to as high-amplitude propagating contractions (HAPCs) in humans and giant migrating contractions in dogs.

Prucalopride does not antagonize 5-$HT_{2A}$, 5-$HT_{2B}$, 5-$HT_3$, motilin or $CCK_1$ receptors or hERG ion channels, with affinity for other receptors or ion channels detected *in vitro* at concentrations exceeding 5-$HT_4$ receptor affinity by 150-fold or greater. Additional *in vitro* studies demonstrated no effect on either contractile responses in human, canine, and porcine coronary arteries at concentrations up to 10 µM (500 times the human clinical $C_{max}$) or on human platelet aggregation at concentrations up to 200 nM (10 times the human clinical $C_{max}$).

In dogs, prucalopride alters colonic motility patterns via serotonin 5-$HT_4$ receptor stimulation: it stimulates proximal colonic motility, enhances gastroduodenal motility and accelerates delayed gastric emptying. Furthermore, giant migrating contractions are induced by prucalopride. These are equivalent to the colonic mass movements in humans, and provide the main propulsive force to defecation. In dogs, the effects observed in the gastrointestinal tract are sensitive to blockade with selective 5-$HT_4$ receptor antagonists illustrating that the observed effects are exerted via selective action on 5-$HT_4$ receptors.

11.1.2 Pharmacodynamic effects

*High amplitude propagating contractions*

The pharmacodynamic effects of prucalopride have been confirmed in human subjects with chronic constipation using manometry in an open-label, randomized, crossover, reader-blinded study investigating the effect of prucalopride 2 mg and an osmotic laxative on colon motility as determined by the number of colonic high-amplitude propagating contractions (HAPCs, also known as giant migrating contractions). Compared with a constipation treatment working through osmotic action, prokinetic stimulation with prucalopride increased colonic motility as measured by the number of HAPCs during the first 12 hours after intake

Pharmacodynamic effects of prucalopride related to prokinetic activity were studied in healthy subjects and in patients with chronic constipation at doses ranging from 0.5-4 mg once daily. In a double-blind, randomized, placebo-controlled, crossover manometry study in healthy subjects receiving prucalopride 4 mg once daily (2 times the maximum human recommended dose of 2 mg) or placebo for 7 days showed that prucalopride increased the amplitude of HAPCs without affecting colonic phasic activity.

*Colonic transit times*

Prucalopride accelerates colonic transit at a dose of 2 mg. An integrated analysis of 3 randomized, placebo-controlled, dose-finding studies in 280 subjects with chronic idiopathic constipation showed that after treatment with prucalopride at once-daily doses of 2 mg or 4 mg (2 times the maximum human recommended dose), the colonic transit time was reduced by 12 hours and 13.9 hours, respectively, compared to an increase of 0.5 hours in the placebo group. Furthermore, a positive correlation between constipation symptom severity and decreased colonic transit time was found.

### 11.2 Pharmacokinetics

11.2.1 Absorption

Prucalopride is rapidly absorbed; after a single oral dose of 2 mg in healthy subjects, $C_{max}$ was attained in 2-3 hours. The absolute oral bioavailability is > 90%. Concomitant intake of food does not influence the oral bioavailability of prucalopride.

11.2.2 Distribution

Prucalopride is extensively distributed, and has a steady-state volume of distribution ($Vd_{ss}$) of 567 litre. The plasma protein binding of prucalopride is about 30%.

11.2.3 Metabolism

Metabolism is not the major route of elimination of prucalopride. *In vitro*, human liver metabolism is very slow and only minor amounts of metabolites are found. Cytochrome P450 3A4 has been shown in vitro to be the only enzyme involved in the metabolism of prucalopride. In an oral dose study with radiolabeled prucalopride in man, small amounts of 7 metabolites were recovered in urine and feces. The quantitatively most important major metabolite in excreta, R107504, accounted for 3.2% and 3.1% of the dose in urine and feces respectively. Other metabolites identified and quantified in urine and feces were R084536 (formed by N-dealkylation) accounting for 3% of the dose and products of hydroxylation (3% of the dose) and N-oxidation (2% of the dose). Unchanged active substance made up 92-94% of the total radioactivity in plasma. R107504, R084536 and R104065 (formed by O-demethylation) were identified as minor plasma metabolites.

11.2.4 Elimination

In healthy subjects a large fraction of the active substance is excreted unchanged (60-65% of the administered dose in urine and about 5% in feces). Renal excretion of unchanged prucalopride involves both passive filtration and active secretion. The plasma clearance of prucalopride averages 317 mL/min. Its terminal half-life is about 1 day. Steady-state is reached within 3-4 days. On once daily treatment with 2 mg prucalopride steady-state plasma concentrations fluctuate between trough and peak values of 2.5 and 7 ng/mL, respectively. The accumulation ratio after once daily dosing ranged from 1.9-2.3. The pharmacokinetics of prucalopride is dose-proportional within and beyond the therapeutic range (tested up to 20 mg). Once daily prucalopride displays time-independent kinetics during prolonged treatment.

A population pharmacokinetic analysis based on combined data from Phase I, II, and III studies showed that the apparent total clearance of prucalopride correlated with creatinine clearance, but not with age, body weight, gender, or race.

## 12. CLINICAL STUDIES

The efficacy of RESOLOR® was established in 3 multicenter, randomized, double-blind, 12-week, placebo-controlled studies in patients with chronic constipation (n = 1279 on RESOLOR®, 1124 females, 155 males). The RESOLOR® doses studied in each of these 3 studies included 2 mg and 4 mg dosing once daily. The primary efficacy endpoint was the proportion (%) of patients that reached normalization of bowel movements defined as an average of 3 or more spontaneous, complete bowel movements (SCBM) per week over the 12-week treatment period. Both doses were statistically superior ($p < 0.001$) to placebo at the primary endpoint in each of the 3 studies, with no incremental benefit of the 4 mg dose over the 2 mg dose.
The proportion of patients treated with the recommended dose of 2 mg RESOLOR® that reached an average of ≥ 3 SCBM per week was 27.8% (week 4) and 23.6% (week 12), vs 10.5% (week 4) and 11.3% (week 12) on placebo. A clinically meaningful improvement of ≥ 1 SCBM per week, the most important secondary efficacy endpoint, was achieved in 48.1% (week 4) and 43.1% (week 12) of patients treated with 2 mg RESOLOR® vs 23.4% (week 4) and 24.6% (week 12) of placebo patients.

In all 3 studies, treatment with RESOLOR® also resulted in significant improvements in the Patient Assessment of Constipation Symptoms (PAC SYM), a validated and disease-specific set of symptom measures including abdominal, stool and rectal symptoms, determined at week 4 and week 12. At the 4- and 12-week assessment time points, significant improvement in several quality of life measures was also observed, such as degree of satisfaction with treatment and bowel habits, physical and psychosocial discomfort and worries and concerns resulting from constipation symptoms.

In addition, the efficacy, safety and tolerability of RESOLOR® in male patients with chronic constipation were evaluated in a 12-week, multi-center, randomized, double-blind, placebo–controlled study (N = 370). The primary endpoint of the study was met: a statistically significantly higher percentage of subjects in the RESOLOR® group (37.9%) had an average of ≥ 3 SCBMs/week compared with subjects in the placebo treatment group (17.7%) ($p < 0.0001$) over the 12-week, double-blind treatment period. The safety profile of RESOLOR® was consistent with that seen in female patients.

The safety and efficacy of RESOLOR® in adult male and female patients (51 male, 450 female) with chronic constipation in the Asia Pacific region (China 62%, South Korea 19%, Australia 8%, Thailand 6%, Taiwan 5%) was evaluated in a 12-week randomized, double- blind, placebo-controlled multi-center study with parallel group design. The primary endpoint of the study was the proportion (%) of patients achieving ≥ 3SCBMs per week during the entire 12 week treatment phase. The key secondary endpoint was the proportion of patients achieving ≥ 3 SCBMs per week during the first 4 weeks of the treatment phase of the study. Results for the primary endpoint in the ITT analysis set showed that the percentage of responders in the RESOLOR® 2 mg group (33.3%) was significantly higher ($p < 0.001$) than that in the placebo group (10.3%). Results for the key secondary endpoint showed that the percentage of responders (34.5%) was significantly higher ($p < 0.001$) than that in the placebo group (11.1%). The overall safety profile in this study was consistent with that established in previous studies with RESOLOR® 2 mg in subjects from Western populations.

It has been shown that Prucalopride does not cause rebound phenomena or induce dependency.

A thorough placebo- and positive-controlled QT study (N=120) was performed to evaluate the effects of RESOLOR® on QT interval at therapeutic (2 mg) and supratherapeutic doses (10 mg). This study did not show significant differences between RESOLOR® and placebo at either dose, based on mean $QT_c$ measurements (largest increase in mean double-delta $QT_c$ [subject-specific correction] was 3.83 msec for 2 mg and 3.03 msec for 10 mg) and outlier analysis. This confirmed the results of two earlier, placebo controlled studies which included QT measurements. The three studies confirm that the incidence of QT-related adverse events and ventricular arrhythmias was low and comparable to placebo.

The efficacy, safety and tolerability of prucalopride in pediatric patients (aged 6 months to 18 years) with functional constipation, were evaluated in an 8-week double-blind, placebo-controlled trial (N = 213), followed by a 16 week open-label comparator-controlled (polyethylene glycol 4000) study of up to 24 weeks (n = 197). The starting dose administered was 0.04 mg/kg/day titrated between 0.02 and 0.06 mg/kg/day (to a maximum of 2 mg daily) for children weighing ≤ 50 kg given as an oral solution of prucalopride or matching placebo. Children weighing > 50 kg received 2 mg/day prucalopride tablets or matching placebo. The primary endpoint of the study was not met: there was no difference in the proportion of patients having an average of ≥ 3 spontaneous bowel movements (SBMs) per week AND an average number of fecal incontinence episodes of ≤ 1 per 2 weeks during week 5 to week 8 of the double-blind treatment period in the Prucalopride and placebo groups, 17% versus 17.8% respectively ($p = 0.9002$). Overall, the safety profile in children was similar to that in adults.

The efficacy and safety of RESOLOR® in patients (aged 18 years or older) with chronic constipation, were evaluated in a 24 week multi-center, randomized, double-blind, placebo- controlled study (N = 361). The proportion of patients with an average weekly frequency of ≥3 Spontaneous Complete Bowel Movements (SCBMs) per week (ie, responders) over the 24-week double-blind treatment phase was not statistically different ($p = 0.367$) between the RESOLOR® (25.1%) and placebo (20.7%) treatment groups. The difference between treatment groups in the average weekly frequency of ≥3 SCBMs per week was not statistically significant over Weeks 1-12 which is inconsistent with the 5 other multi-center, randomized, double-blind, 12-week placebo controlled studies demonstrating efficacy at this timepoint in adult patients. The study is therefore considered to be inconclusive with respect to efficacy.

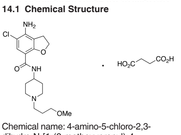
The totality of the data including the other double-blind placebo controlled 12 week studies support the efficacy of RESOLOR®. The safety profile of RESOLOR® in this 24 week study was consistent with that seen in the other 12 week studies.

## 13. NON-CLINICAL STUDIES

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development (including neonatal/juvenile toxicity).

## 14. PHARMACEUTICAL INFORMATION

### 14.1 Chemical Structure




Chemical name: 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide butanedioate

### 14.2 List of Excipients

*Tablet core*
Lactose monohydrate
Microcrystalline cellulose
Colloidal silicon dioxide
Magnesium stearate

*Coating 1 mg tablet*
Hypromellose
Lactose monohydrate
Triacetin
Titanium dioxide (E171)
Macrogol (polyethylene glycol [PEG] 3000)

*Coating 2 mg tablet*
Hypromellose
Lactose monohydrate
Triacetin
Titanium dioxide (E171)
Macrogol (polyethylene glycol [PEG] 3000)
Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (FD&C Blue #2) (E132)

### 14.3 Nature and Content of Container

Aluminium/aluminium perforated unit dose blisters. One box contains 28 film-coated tablets.

### 14.4 Storage

Do not store above 30°C.
Store in the original blister package to protect from moisture.
Keep out of reach of children.

### 14.5 Incompatibilities

None.

### 14.6 Shelf Life

36 months.

### 14.7 Instructions for Use and Handling and Disposal

No special requirements.

## 15. MANUFACTURER

SANICO NV, Veedijk 59, Turnhout, 2300, Belgium

## 16. PRODUCT REGISTRATION HOLDER

DKSH Malaysia Sdn Bhd
B-11-01, The Ascent, Paradigm
No.1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya, Selangor, Malaysia.

## 17. DATE OF REVISION OF THE TEXT

September 2024




AMDIPHARM

| | |
|---|---|
| **AMS** Component No.: | **AW-LF-0001227 (v0.7)** |
| Product Description: | **RESOLOR 1MG 28 TABL. MALAYS., RESOLOR 2MG 28 TABL. MALAYS.** |
| Component: | Leaflet |
| Product Code: | 105278, 105279 |
| Country: | Malaysia |
| Vendor Name: | Sanico NV |
| **Proof Number:** | **0.7** |
| Revision Date: | 09-Dec-2024 |
| Revised by: | PSC |

| | |
|---|---|
| Dimension: | 145 x 780 mm |
| Commodity No.: | N/A |
| Pharma Code: | N/A |
| Print Colours: | Black |
| Non-Print Colours: | Cutter |
| Min. Font Size: | 9 pt |