**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Varuby 90 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of rolapitant (as hydrochloride monohydrate).

Excipient(s) with known effect

This medicinal product contains 230 mg of lactose (as monohydrate) per dose (two tablets).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Tablets are blue, debossed with T0101 on one side and 100 on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prevention of delayed nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy in adults

Varuby is given as part of combination therapy (see section 4.2).

### 4.2 Posology and method of administration

Posology

*Adults*
Varuby is given as part of a regimen that includes dexamethasone and a 5-$HT_3$ receptor antagonist.

180 mg (two tablets) should be administered within 2 hours prior to initiation of each chemotherapy cycle but at no less than 2-week intervals.

There is no medicinal product interaction between rolapitant and dexamethasone, so no dosage adjustment for dexamethasone is required.

The following regimens are recommended for the prevention of nausea and vomiting associated with emetogenic cancer therapy:

*Highly emetogenic chemotherapy regimen*

| | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| Varuby | 180 mg orally;<br>Within 2 hours prior to chemotherapy | None | | |
| Dexamethasone | 20 mg orally;<br>30 min prior to chemotherapy | 8 mg orally twice daily | 8 mg orally twice daily | 8 mg orally twice daily |
| 5-$HT_3$ receptor antagonist | Standard dose of 5-$HT_3$ receptor antagonist. See the Summary of Product Characteristics for the co-administered 5-$HT_3$ receptor antagonist for appropriate dosing information. | None | | |

*Moderately emetogenic chemotherapy regimen*

| | Day 1 | Day 2 | Day 3 | Day 4 |
|---|---|---|---|---|
| Varuby | 180 mg orally;<br>Within 2 hours prior to chemotherapy | None | | |
| Dexamethasone | 20 mg orally;<br>30 min prior to chemotherapy | None | | |
| 5-$HT_3$ receptor antagonist | Standard dose of 5-$HT_3$ receptor antagonist. See the Summary of Product Characteristics for the co-administered 5-$HT_3$ receptor antagonist for appropriate dosing information. | See the Summary of Product Characteristics for the co-administered 5-$HT_3$ receptor antagonist for appropriate dosing information. | | |

Special populations

*Elderly people (≥ 65 years)*
No dose adjustment is necessary for the elderly. Limited data in patients aged 75 years and older are available. Varuby should be used with caution in these patients (see section 5.2).

*Renal impairment*
No dose adjustment is necessary for patients with mild or moderate renal impairment. There are limited data in patients with severe renal impairment and no data in patients with end stage renal disease undergoing haemodialysis. Varuby should be used with caution in these patients (see section 5.2).

*Hepatic impairment*
No dose adjustment is needed in patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment. Varuby should be used with caution in these patients (see sections 4.4 and 5.2).

*Paediatric population*
The safety and efficacy of rolapitant in children and adolescents below 18 years of age has not yet been established. No data are available.

Method of administration

The tablets should be swallowed whole, with some water and may be taken with or without food.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In combination with St John's wort (see section 4.5)

## 4.4 Special warnings and precautions for use

Patients with severe hepatic impairment

There are no data in patients with severe hepatic impairment (see section 5.2). Varuby should be used with caution in these patients. If use cannot be avoided, patients should be monitored for adverse reactions to Varuby (see section 4.8).

Patients with severe renal impairment

There are limited data in patients with severe renal impairment (see section 5.2). Varuby should be used with caution in these patients. If use cannot be avoided, patients should be monitored for adverse reactions to Varuby (see section 4.8).

Interactions

Varuby is not recommended in patients who require chronic administration of strong (e.g. rifampicin, carbamazepine, phenobarbital, enzalutamide, phenytoin) or moderate enzyme inducers (e.g. efavirenz, rifabutin) (see section 4.5)

The efficacy and safety of rolapitant with concurrent use of another $NK_1$ receptor antagonist (e.g. aprepitant and a combination of netupitant and palonosetron hydrochloride) is not established and therefore not recommended (see section 4.5).

Lactose

Varuby contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of Varuby on the pharmacokinetics of other active substances

*CYP2D6 substrates*
Rolapitant is a moderate CYP2D6 inhibitor. Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A 3-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single oral dose of rolapitant and may last longer.

Therefore, caution should be taken when rolapitant is combined with a medicinal product metabolised by CYP2D6, notably those having a narrow therapeutic margin (e.g. propafenone, tamoxifen, metoprolol used in heart failure, thioridazine, pimozide).

*UGT1A1 and UGT2B7 substrates (e.g. irinotecan and morphine, respectively)*
Rolapitant modestly inhibited UGT1A1 and UGT2B7 *in vitro*. Therefore, the potential interactions associated with the inhibition of these UGT enzymes in the intestine cannot be excluded.

*BCRP substrates*

Rolapitant is an inhibitor of Breast-Cancer-Resistance Protein (BCRP). Increased plasma concentrations of BCRP substrates (e.g. methotrexate, irinotecan, topotecan, mitoxantrone, rosuvastatin, sulfasalazine, doxorubicin, bendamustine) may result in potential adverse reactions. Co-administration of a single dose of 180 mg rolapitant with sulfasalazine, a BCRP substrate, resulted in an approximately 2-fold increase in $C_{max}$ and AUC of sulfasalazine. If the combination cannot be avoided, clinical and biological monitoring for adverse reactions related to the concomitant medicinal product must be made. The lowest effective dose of rosuvastatin is to be used.

*P-gp substrates*
Rolapitant is an inhibitor of P-glycoprotein (P-gp). A 70% increase in $C_{max}$ and 30% increase in AUC of digoxin, a P-gp substrate, were observed when administered with a single dose of 180 mg rolapitant. Therefore, clinical monitoring of adverse reactions and, if possible, biological monitoring are recommended when rolapitant is combined with digoxin or with other P-gp substrates (e.g. dabigatran or colchicine), and in particular in patients with renal impairment.

*OATP1B1 and 1B3 substrates*
*In vitro* studies suggest that rolapitant is not expected to inhibit OATP1B1 at clinically relevant concentrations and rolapitant is not an inhibitor of OATP1B3 at the tested concentrations up to 20 µM.

*OCT1 substrates*
*In vitro*, rolapitant is not an inhibitor of OCT1 at the tested concentrations up to 20 µM.

*CYP3A4 substrates*
*In vivo*, rolapitant is not expected to exhibit any inhibitory or inducing effect on CYP3A4. A single dose of 180 mg rolapitant had no significant effects on the pharmacokinetics of midazolam compared to oral midazolam 3 mg alone on Day 1, Day 8 and Day 11.

*Ondansetron*
Rolapitant had no significant effects on the pharmacokinetics of intravenous ondansetron when concomitantly administered with a single 180 mg dose of rolapitant on the same day.

*Dexamethasone*
Rolapitant had no significant effects on the pharmacokinetics of dexamethasone when oral dexamethasone was administered on Days 1 to 3 after a single 180 mg dose of rolapitant was co-administered on Day 1.

*Other CYPs*
No clinically significant interaction is expected with the following medicinal products when administered with a single dose of 180 mg rolapitant on Day 1 and without rolapitant on Day 8: repaglinide 0.25 mg (a CYP2C8 substrate), efavirenz 600 mg (a CYP2B6 substrate), tolbutamide 500 mg (a CYP2C9 substrate) or omeprazole 40 mg (a CYP2C19 substrate).

Rolapitant had no effects on the pharmacokinetics of caffeine (a CYP1A2 substrate) when an oral dose of 200 mg caffeine was administered with a single dose of 180 mg rolapitant on Day 1, and without rolapitant on Day 8 and Day 15.

<u>Effects of other medicinal products on the pharmacokinetics of Varuby</u>

*Enzyme inducers*
Concomitant administration of rifampicin, a strong enzyme inducer significantly decreased the systemic exposure to rolapitant and to its active metabolite. When 600 mg rifampicin was administered once daily for 7 days before and 7 days after administration of a single dose of 180 mg rolapitant, the mean AUC was reduced by 87% and its active metabolite by 89% compared to administration of rolapitant alone. Varuby in patients who require chronic administration of strong

inducers (e.g. rifampicin, carbamazepine, enzalutamide, phenytoin) is not recommended (see section 4.4).

The effect of moderate inducers (e.g. efavirenz, rifabutin) is not established; therefore, the use of rolapitant in patients already given a moderate inducer is not recommended (see section 4.4).

Due to its strong inducing effect, St John's wort is contraindicated with rolapitant (see section 4.3).

*CYP3A4 inhibitors*
No clinically significant effect was seen on the pharmacokinetics of rolapitant when ketoconazole, a strong CYP3A4 inhibitor was administered with rolapitant. Concurrent administration of 400 mg ketoconazole once daily for 21 days following a single 90 mg dose of rolapitant, did not significantly affect the $C_{max}$ of rolapitant while the AUC increased by 21%. This is not expected to be clinically relevant.

Other interactions

The efficacy and safety of rolapitant with concurrent use of another $NK_1$ receptor antagonist (e.g. aprepitant and a combination of netupitant and palonosetron hydrochloride) is not established and therefore not recommended (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no available data on rolapitant use in pregnant women. Studies in animals have shown no teratogenic or embryo-foetal effects. In the pre- and postnatal developmental study, at a dose equivalent to half of the recommended human dose, there was a decrease in memory in female pups in a maze test and a decrease in pup body weight (see section 5.3). Varuby should not be used during pregnancy unless clearly necessary.

Breast-feeding

There are no data on the presence of rolapitant in human milk. Rolapitant administered orally to lactating female rats was present in milk. Breast-feeding is not recommended during treatment with Varuby.

Fertility

Rolapitant did not affect the fertility or general reproductive performance of male rats. Decreases in the number of corpora lutea and implantation sites were observed in the female rat fertility and early embryonic development study (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Varuby has minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of rolapitant (see section 4.8).

## 4.8 Undesirable effects

Summary of safety profile

Over 4,375 patients have been treated with Varuby or a comparator across Phase 1, 2, and 3 clinical studies. A total of 2,798 subjects received oral rolapitant at any dose, including 1,567 subjects in the CINV (chemotherapy-induced nausea and vomiting) studies.

The most common adverse reactions were fatigue (1.9%) and headache (1.5%). The safety profile in the multiple-cycle extensions of highly and moderately emetogenic chemotherapy studies for up to 6 cycles of chemotherapy is similar to the profile observed in Cycle 1.

Tabulated list of adverse reactions

The following adverse reactions were observed in a pooled analysis of the Highly Emetogenic Chemotherapy (HEC) and Moderately Emetogenic Chemotherapy (MEC) studies.

Frequencies are defined as: Very common (≥1/10); common (≥1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known: frequency cannot be estimated from the available data.

| **Adverse reactions per system organ class** | | | |
|---|---|---|---|
| **System organ class** | **Common** | **Uncommon** | **Rare** |
| Infections and infestations | | Oral fungal infection | Candidiasis<br>Oral candidiasis |
| Blood and lymphatic system disorders | | Neutropenia | International Normalised Ratio increased<br>Leukopenia<br>Neutrophil count decreased<br>Thrombocytopenia |
| Immune system disorders | | | Hypersensitivity |
| Metabolism and nutrition disorders | | Decreased appetite | Dehydration<br>Hypomagnesaemia |
| Psychiatric disorders | | Insomnia | Anxiety<br>Bruxism |
| Nervous system disorders | Headache | Dizziness<br>Disturbance in attention<br>Dysgeusia<br>Somnolence | Balance disorder<br>Movement disorder<br>Syncope |
| Ear and labyrinth disorders | | | Hypoacusis<br>Tinnitus |
| Eye disorders | | | Vision blurred |
| Cardiac disorders | | | Heart rate increased |
| Gastrointestinal disorders | Constipation | Diarrhoea<br>Dyspepsia<br>Nausea<br>Abdominal distension<br>Abdominal pain<br>Stomatitis | Abdominal discomfort<br>Change of bowel habit<br>Dry mouth<br>Gastrooesophageal reflux disease<br>Retching |
| Vascular disorders | | | Hypertension |
| Respiratory, thoracic and mediastinal disorders | | Hiccups | Dyspnoea |
| Skin and subcutaneous tissue disorders | | | Alopecia<br>Angioedema<br>Dermatitis acneiform<br>Dry skin |
| Musculoskeletal and connective tissue disorders | | Myalgia | Arthralgia<br>Back pain<br>Muscular weakness<br>Rhabdomyolysis |

| Adverse reactions per system organ class | | | |
|---|---|---|---|
| **System organ class** | **Common** | **Uncommon** | **Rare** |
| General disorders and administration site conditions | Fatigue | Asthenia | Gait disturbance |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

### 4.9 Overdose

Rolapitant doses up to 720 mg have been used in clinical studies without any safety concerns. In case of overdose, the medicinal product should be discontinued and general supportive treatment and monitoring should be provided. Because of the antiemetic activity of rolapitant, emesis induced by a medicinal product may not be effective. Dialysis studies have not been performed.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, other antiemetics, ATC code: A04AD14

Mechanism of action

Rolapitant is a selective antagonist of human substance P/neurokinin 1 ($NK_1$) receptors.

Clinical efficacy and safety

*Cisplatin-Based Highly Emetogenic Chemotherapy (HEC)*

*Study 1 and Study 2 (HEC)*

In two multicentre, randomised, double-blind, parallel group, controlled clinical studies (Study 1 and Study 2), the rolapitant regimen (180 mg rolapitant, 10 mcg/kg intravenous granisetron and 20 mg oral dexamethasone) was compared with control therapy (placebo, 10 mcg/kg intravenous granisetron and 20 mg oral dexamethasone) on Day 1 in patients receiving a chemotherapy regimen that included cisplatin ≥60 mg/m$^2$. On Day 2 to 4, patients received 8 mg twice daily of oral dexamethasone. Study medicinal products were administered prior to chemotherapy on Day 1 at the following intervals: rolapitant (1 to 2 hours prior); granisetron and dexamethasone (30 minutes prior).

A total of 1087 patients were randomised to either the rolapitant regimen (N=544) or control therapy (N=543) across Study 1 and Study 2; 1070 patients were included in the evaluation of efficacy; 37% were women and 63% were men. Of the 1070 patients, 26% were greater than 65 years of age and 3% were greater than 75 years of age.

The primary endpoint in both studies was complete response (defined as no emetic episodes and no rescue medicinal product) in the delayed phase (>24 to 120 hours) of chemotherapy-induced nausea and vomiting. The following additional pre-specified endpoints were also evaluated: complete response in the acute phase (0 to 24 hours) and overall phase (0 to 120 hours); no emesis in each

CINV phase, no significant nausea in each CINV phase, and time to first emesis or use of rescue medicinal product.

The results were evaluated for each individual study and for the two studies combined. Individual results from Studies 1 and 2 as well as a summary of the key results from the combined analysis are shown in Table 1 below.

**Table 1: Proportion of patients receiving cisplatin chemotherapy responding by treatment group and phase (Studies 1 and 2 – HEC Individual Results)**

| Efficacy Endpoints[a] | HEC Study 1 | | | HEC Study 2 | | | Study 1 and 2 Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rolapitant (N=264) Rate (%) | Control (N=262) Rate (%) | P-Value[b] | Rolapitant (N=271) Rate (%) | Control (N=273) Rate (%) | P-Value[b] | Rolapitant (N=535) Rate (%) | Control (N=535) Rate (%) | P-Value[c] |
| **Complete Response** | | | | | | | | | |
| Delayed | 72.7 | 58.4 | <0.001 | 70.1 | 61.9 | 0.043 | 71.4 | 60.2 | <0.001 |
| Acute | 83.7 | 73.7 | 0.005 | 83.4 | 79.5 | N.S. | 83.6 | 76.6 | 0.004 |
| Overall | 70.1 | 56.5 | 0.001 | 67.5 | 60.4 | N.S. | 68.8 | 58.5 | <0.001 |
| **No Emesis** | | | | | | | | | |
| Acute | 86.4 | 76.0 | 0.002 | 85.6 | 81.7 | N.S. | 86.0 | 78.9 | 0.002 |
| Delayed | 78.0 | 61.8 | <0.001 | 73.1 | 65.2 | 0.046* | 75.5 | 63.6 | <0.001 |
| Overall | 75.4 | 59.2 | <0.001 | 70.8 | 64.1 | N.S. | 73.1 | 61.7 | <0.001 |
| **No Significant Nausea** | | | | | | | | | |
| Acute | 86.4 | 79.4 | 0.035 | 90.0 | 85.7 | N.S. | 88.2 | 82.6 | 0.009 |
| Delayed | 73.5 | 64.9 | 0.034 | 74.5 | 68.9 | N.S. | 74.0 | 66.9 | 0.011 |
| Overall | 71.6 | 63.0 | 0.037 | 72.7 | 67.8 | N.S. | 72.1 | 65.4 | 0.017 |

[a] Primary endpoint was complete response in the delayed phase. Delayed phase: >24 to 120 hours post-cisplatin treatment; Acute phase: 0 to 24 hours post-cisplatin treatment; Overall phase: 0 to 120 hours post-cisplatin treatment

[b] Unadjusted P-values are obtained from Cochran-Mantel Haenszel test, stratified for sex.

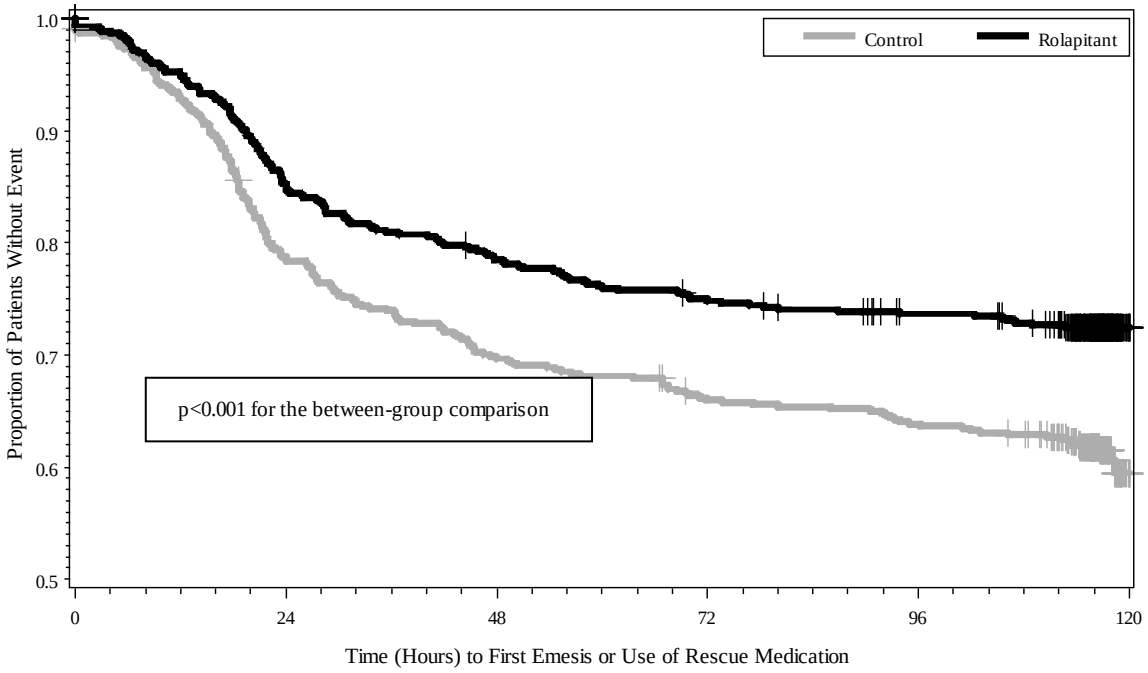
[c] Unadjusted P-values are obtained from Cochran-Mantel-Haenszel test, stratified by study and sex.

N.S.=Not significant (p>0.05)

*Not significant after applying pre-specified multiplicity adjustment.

The estimated time to first emesis in the combined analysis is depicted by the Kaplan-Meier plot in **Figure 1**.

**Figure 1**: Kaplan-Meier Plot of Proportions of Patients without Emesis or Use of Rescue Medication (Study 1 and Study 2 Combined – HEC)




*Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide Chemotherapy*

*Study 3 (MEC)*

In Study 3, a multicentre, randomised, double-blind, parallel group, controlled clinical study in moderately emetogenic chemotherapy, the rolapitant regimen (180 mg rolapitant, 2 mg oral granisetron and 20 mg oral dexamethasone) was compared with control therapy (placebo, 2 mg oral granisetron and 20 mg oral dexamethasone) on Day 1 in patients receiving a moderately emetogenic chemotherapy regimen that included 53% of patients receiving a combination of anthracycline and cyclophosphamide (AC). On Day 2 to 3, patients received 2 mg once daily of oral granisetron. Study medicinal products were administered prior to chemotherapy on Day 1 at the following intervals: rolapitant (1 to 2 hours prior); granisetron and dexamethasone (30 minutes prior). At the time the study was designed, AC containing chemotherapy regimens were considered to be moderately emetogenic. Recent guidance has updated these regimens to highly emetogenic. The percentage of patients who received carboplatin in Cycle 1 was 30%.

A total of 1369 patients were randomised to either the rolapitant regimen (N=684) or control therapy (N=685). A total of 1332 patients were included in the evaluation of efficacy, 80% were women and 20% were men. Of these 1332 patients, 28% were greater than 65 years of age and 6% were greater than 75 years of age. Of these 1332 patients, 629 received non-AC chemotherapy.

The primary endpoint was complete response (defined as no emetic episodes and no rescue medicinal product) in the delayed phase (>24 to 120 hours) of chemotherapy-induced nausea and vomiting. The following additional pre-specified endpoints were also evaluated: complete response in the acute phase (0 to 24 hours) and overall phase (0 to 120 hours); no emesis in each CINV phase, no significant nausea in each CINV phase and time to first emesis or use of rescue medicinal product.

A summary of the study results from the MEC Study (Study 3) is shown in Table 2 below. A summary of the results from the non-AC and AC subsets are provided in Table 3.

| **Table 2: Proportion of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase** | | | |
|---|---|---|---|
| | **Study 3 – MEC** | | |
| **Efficacy Endpoints**[a] | **Rolapitant (N=666) Rate (%)** | **Control (N=666) Rate (%)** | **P-Value**[b] |
| **Complete Response** | | | |
| Delayed | 71.3 | 61.6 | <0.001 |
| Acute | 83.5 | 80.3 | N.S. |
| Overall | 68.6 | 57.8 | <0.001* |
| **No Emesis** | | | |
| Acute | 87.8 | 84.5 | N.S. |
| Delayed | 80.5 | 69.8 | <0.001* |
| Overall | 78.7 | 65.3 | <0.001* |
| **No Significant Nausea (maximum VAS <25 on 0-100 scale)** | | | |
| Acute | 82.1 | 84.7 | N.S. |
| Delayed | 72.7 | 69.4 | N.S. |
| Overall | 70.6 | 66.5 | N.S. |

[a] Primary endpoint was complete response in the delayed phase. Acute phase: 0 to 24 hours after AC or non-AC regimen; Delayed phase: >24 to 120 hours after AC or non-AC regimen; Overall phase: 0 to 120 hours after AC or non-AC regimen

[b] Unadjusted P-values are obtained from Cochran-Mantel-Haenszel test, stratified by sex. N.S.=Not significant (p>0.05)

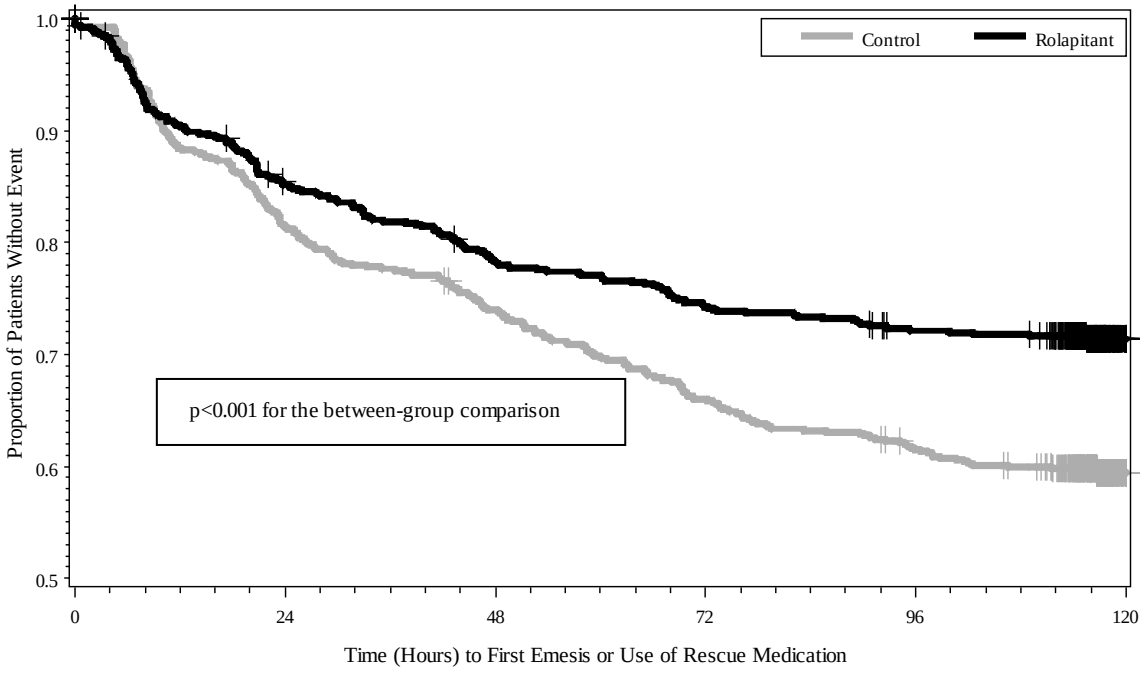
* N.S. after pre-specified multiplicity adjustment.

| **Table 3: Proportion of Patients Receiving AC or non-AC Chemotherapy Achieving Complete Response** | | | |
|---|---|---|---|
| **Complete Response** | **Rolapitant** | **Control** | **P-Value**[a] |
| **Non-AC** | **N=322** | **N=307** | |
| Delayed | 76.1 | 63.8 | <0.001 |
| Acute | 90.7 | 84.4 | 0.016 |
| Overall | 74.8 | 61.2 | <0.001 |
| **AC** | **N=344** | **N=359** | |
| Delayed | 66.9 | 59.6 | 0.047 |
| Acute | 76.7 | 76.9 | N.S. |
| Overall | 62.8 | 54.9 | 0.033 |

[a] Unadjusted P-values are obtained from Cochran-Mantel-Haenszel test. N.S.=Not significant (p>0.05)

The estimated time to first emesis or use of rescue medicinal product in patients receiving a MEC regimen is depicted by the Kaplan-Meier plot in Figure 2.

**Figure 2**: Kaplan-Meier Plot of Proportions of Patients without Emesis or Use of Rescue Medication (Study 3--MEC)




The impact of nausea and vomiting on patients' daily lives was assessed using the Functional Living Index-Emesis (FLIE). The proportion of patients with no impact on daily life was higher in the Varuby group than in the control group (MEC: 73.2% vs. 67.4%; p=0.027).

*Multiple-Cycle Extension:* In each study, patients had the option of continuing into a multiple-cycle extension for up to 5 additional cycles of chemotherapy receiving the same treatment as assigned in cycle 1. At Day 6 to 8 following initiation of chemotherapy, patients were asked to recall whether they had any episode of vomiting or retching or nausea that interfered with normal daily life. Antiemetic activity of rolapitant was maintained throughout repeat cycles for those patients continuing in each of the multiple cycles.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with rolapitant in all subsets of the paediatric population in prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cisplatin-based cancer therapy and moderately emetogenic cancer therapy (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Rolapitant displays linear PK with exposures increased in a dose-proportional manner. Rolapitant is slowly eliminated with a mean terminal half-life of approximately 7 days. Rolapitant is eliminated mainly through the hepatobiliary route, with minor contributions from renal elimination. Rolapitant is metabolised by CYP3A4 to form a major active metabolite, M19. *In vitro* studies suggest that rolapitant is not an inhibitor of CYP2E1.

Absorption

Following a single dose administration of 180 mg rolapitant under fasting conditions to healthy subjects, rolapitant was measurable in plasma between 30 minutes and the peak plasma concentration ($C_{max}$) for rolapitant which was reached in about 4 hours and mean $C_{max}$ was 968 ng/mL (%CV:28%).

Following multiple oral doses 9 to 45 mg once daily of rolapitant; accumulation of rolapitant was approximately 5-fold.

The systemic exposures ($C_{max}$ and AUC) to rolapitant increased in a dose-proportional manner when the dose of rolapitant increased from 4.5 mg to 180 mg. With an increase in dose by 4 times from the recommended clinical dose of 180 mg, the $C_{max}$ and AUC of rolapitant increased by 3.1 fold and 3.7 fold, respectively.

The absolute bioavailability of rolapitant is approximately 100%, indicating minimal first pass effect.

Concomitant administration of a high fat meal did not significantly affect the pharmacokinetics of rolapitant after administration of 180 mg rolapitant.

Distribution

Rolapitant was highly protein bound to human plasma (99.8%). The apparent volume of distribution (Vd/F) was 460 L in healthy subjects, indicating an extensive tissue distribution of rolapitant. In a population pharmacokinetic analysis of rolapitant, the Vd/F was 387 L in cancer patients.

Biotransformation

Rolapitant is metabolised by CYP3A4 to form a major active metabolite, M19 (C4-pyrrolidine-hydroxylated rolapitant). In a mass balance study, the metabolite M19 was the major circulating metabolite. The formation of M19 was significantly delayed with the median $T_{max}$ of 120 hours (range: 24-168 hours) and the mean half-life of M19 was 158 hours. The exposure ratio of M19 to rolapitant was approximately 50% in plasma.

Elimination

Following single oral doses (4.5 to 180 mg) of rolapitant, the mean terminal half-life ($t_{1/2}$) of rolapitant ranged from 169 to 183 hours (approximately 7 days) and was independent of dose. In a population pharmacokinetic analysis the apparent total clearance (CL/F) of rolapitant was 0.96 L/hour in cancer patients.

Rolapitant is eliminated primarily through the hepatobiliary route. Following administration of a single oral 180-mg dose of [$^{14}$C]-rolapitant, on average 14.2% (range 9% to 20%) and 73% (range 52% to 89%) of the dose was recovered in the urine and feces, respectively over 6 weeks. In pooled samples collected over 2 weeks, 8.3% of the dose was recovered in the urine primarily as metabolites and 37.8% of the dose was recovered in the feces primarily as unchanged rolapitant. Unchanged rolapitant or M19 were not found in pooled urine sample. Drug metabolising enzymes (and drug transporters) other than CYP3A4 involved in rolapitant hepatobiliary elimination remain to be elucidated.

Pharmacokinetics in special populations

*Age, Sex and Race/Ethnicity*
Population pharmacokinetic analyses indicated that age, sex and race had no significant impact on the pharmacokinetics of Varuby. There are limited data in patients aged 75 years and older.

*Hepatic Impairment*
Following administration of a single dose of 180 mg rolapitant to patients with mild hepatic impairment (Child-Pugh Class A), the pharmacokinetics of rolapitant were comparable with those of healthy subjects. In patients with moderate hepatic impairment (Child-Pugh Class B), the mean $C_{max}$ was 25% lower while mean AUC of rolapitant was similar compared to those of healthy subjects. The median $T_{max}$ for M19 was delayed to 204 hours in patients with mild or moderate hepatic impairment

compared to 168 hours in healthy subjects. The pharmacokinetics of Varuby was not studied in patients with severe hepatic impairment (Child-Pugh Class C).

*Renal Impairment*
In population pharmacokinetic analyses, creatinine clearance (CLcr) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CLcr: 60 to 90 mL/min) or moderate (CLcr: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal impairment. The pharmacokinetics of Varuby was not studied in patients with end-stage renal disease requiring haemodialysis.

Relationship between concentration and effect

*$NK_1$ Receptor Occupancy*
A human Positron Emission Tomography (PET) study with rolapitant demonstrated that rolapitant crosses the blood brain barrier and occupies brain $NK_1$ receptors. A dose-dependent increase in mean $NK_1$ receptor occupancy was observed in the dose range from 4.5 mg to 180 mg of rolapitant. At rolapitant plasma concentrations of >15 ng/mL and 348 ng/mL, the $NK_1$ receptor occupancies in the cortical regions were approximately >50% and 90% respectively. At the 180 mg dose of rolapitant, the mean $NK_1$ receptor occupancy in the cortical regions was greater than 90% for at least 120 hours.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, teratogenic potential, and carcinogenic potential.

The mechanism of the significant difference of half-lives observed between the rat and monkey (6-8 h) and human (7 days) is not elucidated.

In rodents, rolapitant was tested in repeated dose oral toxicity studies up to 26 weeks in duration, and the liver, thyroid, kidneys, epididymis and uterus were identified as target organs. In a three-month rat study, clonic convulsions were observed in a single animal at 125 mg/kg/day (approximately 6 times the recommended human dose on a body surface area basis). In the one-month monkey study, convulsions were observed at 60 mg/kg/day (approximately 5.8 times the recommended human dose on a body surface area basis). The relevance of convulsions for humans is unknown.

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose equivalent to 9 mg/kg per day free base (approximately 0.5 times the recommended human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose equivalent to 4.5 mg/kg per day free base (approximately 0.2 times the recommended human dose on a body surface area basis), there were decreases in the number of corpora lutea and implantation sites.

In a pre- and post-natal development rat study, maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg per day free base (approximately 1.2 times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg per day rolapitant free base (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

Based on the environmental risk assessment, rolapitant is considered as very persistent, bioaccumulative and not readily biodegradable.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet content

Lactose monohydrate
Pregelatinised starch
Microcrystalline cellulose (E460)
Povidone (K-30)
Croscarmellose sodium
Colloidal silicon dioxide
Magnesium stearate

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine (E132)
Polysorbate 80

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Polyvinyl chloride/polychlorotrifluoroethylene/aluminium foil twinned blister.
Pack size of two tablets.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1180/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2017

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Manufacturing Packaging Farmaca (MPF) B.V.
Appelhof 13
NL-8465 RX Oudehaske
Netherlands

Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12
NL-8448 CN Heerenveen
Netherlands

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

**Wallet card, each containing 2 film-coated tablets – WITH BLUE BOX**

## 1. NAME OF THE MEDICINAL PRODUCT

Varuby 90 mg film-coated tablets
Rolapitant

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 90 mg of rolapitant.

## 3. LIST OF EXCIPIENTS

Also contains lactose. See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Single dose = 2 tablets

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/17/1180/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

VARUBY

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Varuby 90 mg tablets
Rolapitant

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

TESARO Bio Netherlands B.V.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Varuby 90 mg film-coated tablets**
Rolapitant

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Varuby is and what it is used for

**What Varuby is**
Varuby contains the active substance rolapitant.

**What Varuby is used for**
Varuby is used to help prevent adults with cancer feeling sick (nauseous) or being sick (vomiting) while having cancer treatment chemotherapy.

**How Varuby works**
Chemotherapy can cause the body to release “substance P.”
Substance P attaches to nerve cells in the brain’s vomiting centre and makes you feel sick or be sick. Rolapitant, the active substance in Varuby, blocks substance P from attaching to these nerve cells and this helps prevent nausea and vomiting.

## 2. What you need to know before you take Varuby

**Do not take Varuby:**
- if you are allergic to rolapitant or any of the other ingredients of this medicine (listed in section 6).
- if you take an herbal medicine called St John’s wort *(Hypericum performatum)*, used to treat depression and difficulty sleeping (see section 2 under ‘Other medicines and Varuby’).

If you are not sure, talk to your doctor, pharmacist or nurse before taking this medicine.

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before taking this medicine if:

- you have severe liver or kidney problems
- you need to take certain medicines which may reduce the effectiveness of Varuby, such as:
  - rifampicin, to treat tuberculosis and other infections
  - carbamazepine, to treat epilepsy and nerve pain
  - phenobarbital, to treat epilepsy
  - enzalutamide, to treat prostate cancer
  - phenytoin, to treat epilepsy
  - efavirenz, to treat human immunodeficiency virus (HIV)
  - rifabutin, to treat tuberculosis and other infections
  - other medicines that contain an $NK_1$ antagonist, such as aprepitant and a combination of netupitant and palonosetron hydrochloride (for the prevention of nausea and vomiting associated with cancer chemotherapy) (see section 2 under 'Other medicines and Varuby')

**Children and adolescents**
Varuby should not be taken by children and adolescents under 18 years because it has not been studied in this group.

**Other medicines and Varuby**
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. Varuby may affect how some other medicines work. These include:
- propafenone (used to treat irregular or abnormal heart beat)
- tamoxifen (used to treat breast cancer)
- metoprolol (used to treat high blood pressure and heart conditions)
- thioridazine (used to treat psychiatric conditions like schizophrenia)
- pimozide (used to treat psychiatric conditions like schizophrenia)
- morphine (used to treat moderate to severe pain)
- methotrexate (used to treat cancer, psoriasis, and rheumatoid arthritis)
- irinotecan (used to treat cancer)
- topotecan (used to treat cancer)
- mitoxantrone (used to treat cancer)
- sulfasalazine (used to treat bowel disease and rheumatoid arthritis)
- doxorubicin (used in cancer chemotherapy)
- bendamustine (used in the treatment of leukaemia)
- digoxin (used to treat heart conditions)
- dabigatran (used to prevent blood clots)
- colchicine (used to treat gout)
- medicines called 'statins,' such as atorvastatin, fluvastatin, rosuvastatin and simvastatin, that are used in the treatment of high levels of fats (such as cholesterol) in the blood
- bosentan (used to treat high blood pressure in the pulmonary artery)
- fexofenadine (used to treat allergy symptoms)

**Pregnancy and breast-feeding**
There is no information on the effects of this medicine if taken during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

It is not known whether Varuby is present in milk; therefore, breast-feeding is not recommended during treatment with this medicine. It is important that you tell your doctor if you are breast-feeding or are planning to breast-feed before taking this medicine.

**Driving and using machines**
Varuby has minor influence on your ability to drive and use machines. You may feel dizzy or tired after taking this medicine. If this happens, do not drive or use any tools or machines.

**Varuby contains lactose**
Each dose (two tablets) contains 230 mg of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. How to take Varuby

Always take this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

**How much to take**
- The recommended dose is 180 mg (two 90 mg tablets). Swallow the tablets whole, with some water.
- Take the tablets within 2 hours before you start your chemotherapy cycle.
- You can take Varuby with or without food.

Taking Varuby before chemotherapy prevents sickness and feelings of sickness. Do not take this medicine in the days after you have chemotherapy - unless you are about to have another chemotherapy cycle. Do not take Varuby more than once every two weeks.

**If you take more Varuby than you should**
The usual dose is two tablets. If you think you may have taken more than you should, tell your doctor straight away.

**If you forget to take Varuby**
If you have forgotten to take your dose, tell your doctor straight away.

**If you stop taking Varuby**
Varuby helps prevent feeling sick and being sick when you have chemotherapy. If you do not want to take this medicine, discuss this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

**Serious side effects:**
Rare: may affect up to 1 in 1,000 people
If you have symptoms of an allergic reaction, such as sudden shortness of breath, swelling of the lips or tongue or change in taste, swelling of skin or tissue or sudden rash or fever, or faster heartbeats, **tell your doctor or nurse immediately**. They will provide appropriate treatment.

**Other side effects:**

Common: may affect up to 1 in 10 people
- headache
- constipation
- feeling tired

Uncommon: may affect up to 1 in 100 people
- sore or painful muscles

- feeling dizzy, difficulty concentrating, lack of energy, feeling sleepy (somnolence) or trouble sleeping (insomnia)
- stomach problems including stomach discomfort, bloating, nausea, pain, indigestion, and diarrhoea
- low levels of white blood cells which fight infections (shown in blood tests)
- infection in the mouth
- mouth sores
- decreased appetite
- hiccups
- weakness

Rare: may affect up to 1 in 1,000 people
- thrush in the mouth or skin
- a reduction in number of platelets (shown in blood tests)
- increased risk of bleeding
- decrease in white blood cells that fight infections (shown in blood tests)
- dehydration
- low levels of magnesium in the blood (shown in blood tests)
- feelings of worry or fear, restlessness
- teeth grinding
- losing your balance
- difficulty in moving
- passing out or the feeling of nearly passing out
- partial loss of hearing
- ringing in the ears
- blurry vision
- heart rate increased
- stomach discomfort
- change in bowel habit
- dry mouth
- acid reflux or heartburn
- gagging or sensation of throwing up
- high blood pressure
- hair loss
- skin rash, similar to acne
- dry skin
- pain in joint
- back pain
- muscle weakness
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown (a condition called rhabdomyolysis).
- problems walking

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Varuby

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Varuby contains**
The active substance is rolapitant. Each tablet contains 90 mg of rolapitant.

The other ingredients are:
- Tablet core: lactose monohydrate (see section 2 under 'Varuby contains lactose'), pregelatinised starch, microcrystalline cellulose (E460), povidone (K-30), croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.

- Film-coat: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc, indigo carmine (E132), and polysorbate 80.

**What Varuby looks like and contents of the pack**
The tablets are blue, debossed with T0101 on one side and 100 on the other side.

Pack size of two tablets in a polyvinyl chloride/polychlorotrifluoroethylene/aluminium foil twinned blister.

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Manufacturing Packaging Farmaca (MPF) B.V.
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Netherlands

TESARO Bio Netherlands B.V.
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**This leaflet was last revised in <{MM/YYYY}>.**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu