ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Yuvanci 10 mg/20 mg film-coated tablets
Yuvanci 10 mg/40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Yuvanci 10 mg/20 mg film-coated tablets

Each film-coated tablet contains 10 mg of macitentan and 20 mg of tadalafil.

Yuvanci 10 mg/40 mg film-coated tablets

Each film-coated tablet contains 10 mg of macitentan and 40 mg of tadalafil.

Excipient(s) with known effect

Each 10 mg/20 mg film-coated tablet contains approximately 147 mg of lactose (as monohydrate).

Each 10 mg/40 mg film-coated tablet contains approximately 253 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yuvanci 10 mg/20 mg film-coated tablets

Pink, oblong, 13 mm × 6 mm film-coated tablets debossed with “1020” on one side and “MT” on the other side.

Yuvanci 10 mg/40 mg film-coated tablets

White to almost white, oblong, 15 mm × 7 mm film-coated tablets debossed with “1040” on one side and “MT” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yuvanci is indicated as substitution therapy for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, who are already treated with the combination of macitentan and tadalafil given concurrently as separate tablets.

4.2 Posology and method of administration

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Posology

The recommended dose of Yuvanci is one 10 mg/40 mg tablet taken orally once daily.

- For patients who are currently treated with 10 mg macitentan and 40 mg tadalafil as separate tablets use Yuvanci 10 mg/40 mg tablet
- For patients who are currently treated with 10 mg macitentan and 20 mg tadalafil as separate tablets use Yuvanci 10 mg/20 mg tablet. The dose may be increased to 10/40 mg once per day, based on tolerability.

Yuvanci should be taken every day at about the same time**.**

Missed dose

If the patient misses a dose of Yuvanci, the patient should take it as soon as possible and then take the next dose at the regularly scheduled time. The patient should not take two doses at the same time if a dose has been missed.

Special populations

Elderly
No dose adjustment is required in patients over the age of 65 years (see section 5.2).

Renal impairment
The use of Yuvanci is not recommended in patients undergoing dialysis or in patients with severe renal impairment (creatinine clearance <30 ml/min). No need to adjust dose for patients with mild to moderate renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
Yuvanci is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C), or clinically significant elevated hepatic aminotransferases greater than 3 times the upper limit of normal (> 3×ULN) (see section 4.3). No need to adjust dose for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of Yuvanci in children and adolescents below 18 years have not been studied. No data are available.

Method of administration

For oral use.

The film-coated tablets are not breakable and are to be swallowed whole with water, with or without food. The impact of breaking or grinding was not investigated.

4.3 Contraindications

- Hypersensitivity to any of the active substances, or to any of the excipients listed in section 6.1.
- Acute myocardial infarction within the last 90 days.
- Pregnancy (see sections 4.4 and 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 4.6).
- Breastfeeding (see section 4.6).
- Patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C) (see sections 4.2 and 4.4).

- Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) > 3 × ULN) (see sections 4.2 and 4.4).
- Severe hypotension (<90/50 mm Hg).
- Co-administration with nitrates or guanylate cyclase stimulators (such as riociguat, see section 4.5).
- Patients with a history of non-arteritic anterior ischaemic optic neuropathy (NAION).

4.4 Special warnings and precautions for use

Liver function

Elevations of liver aminotransferases (AST and ALT) have been associated with PAH and with endothelin receptor antagonists (ERAs) (see section 4.8). Yuvanci is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (Child-Pugh Class C) or elevated hepatic aminotransferases greater than 3 times the upper limit of normal (> 3 × ULN). Liver enzyme tests should be obtained prior to initiation of Yuvanci (see sections 4.2 and 4.3).

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of liver injury (e.g., jaundice), Yuvanci treatment should be discontinued.

Reinitiation of Yuvanci may be considered following the return of hepatic enzyme levels to within the normal range in patients who have not experienced clinical symptoms of liver injury. The advice of a hepatologist is recommended.

Use in women of childbearing potential

Yuvanci treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.6). Women should not become pregnant for 1 month after discontinuation of Yuvanci. Monthly pregnancy tests during treatment with Yuvanci are recommended to allow the early detection of pregnancy.

Haemoglobin concentration

Decrease in haemoglobin concentrations has been associated with endothelin receptor antagonists (ERAs) including macitentan (see section 4.8). In placebo-controlled studies, macitentan-related decreases in haemoglobin concentration were not progressive, stabilised after the first 4-12 weeks of treatment and remained stable during chronic treatment. Cases of anaemia requiring blood cell transfusion have been reported with macitentan and other ERAs. Initiation of Yuvanci is not recommended in patients with severe anaemia. It is recommended that haemoglobin concentrations be measured prior to initiation of treatment with Yuvanci, and tests repeated during treatment as clinically indicated.

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when Yuvanci is administered in patients with PAH, the possibility of pulmonary veno-occlusive disease should be considered. Since there are no clinical data on administration of Yuvanci to patients with veno-occlusive disease, administration of Yuvanci to such patients is not recommended.

Vision

Visual defects, including central serous chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Most cases of CSCR

resolved spontaneously after stopping tadalafil. Regarding NAION, analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to tadalafil or other PDE5 inhibitors. All patients taking Yuvanci should be advised that in case of sudden visual defect, visual acuity impairment and/or visual distortion, to stop taking Yuvanci and consult a physician immediately (see section 4.3). Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical studies, and use in these patients is not recommended.

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension, previous hearing loss history and associated connective tissue diseases) patients should be advised to seek prompt medical attention in the event of sudden decrease or loss of hearing.

Priapism and anatomical deformation of the penis

Priapism has been reported in men treated with PDE5 inhibitors. Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result. Yuvanci should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

Renal impairment

There is no experience with the use of Yuvanci in patients undergoing dialysis, therefore Yuvanci is not recommended in this population. The use of Yuvanci in patients with severe renal impairment is not recommended (see sections 4.2 and 5.2) Patients with renal impairment may have a higher risk of experiencing hypotension and anaemia during treatment with macitentan. Therefore, monitoring of blood pressure and haemoglobin should be considered during use with Yuvanci.

Interactions

Use of Yuvanci should be avoided in patients chronically taking potent CYP3A4 inducers and is not recommended in patients taking concomitant potent inhibitors of CYP3A4. Caution should be exercised when Yuvanci is administered concomitantly with both a moderate CYP3A4 and CYP2C9 inhibitor (see section 4.5).

Cardiovascular conditions

Use of Yuvanci is not recommended in patients with any of the following cardiovascular conditions since there are no clinical data.

- clinically significant aortic and mitral valve disease
- pericardial constriction
- restrictive or congestive cardiomyopathy
- significant left ventricular dysfunction
- life-threatening arrhythmias
- symptomatic coronary artery disease
- uncontrolled hypertension.

Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Physicians should carefully consider whether their patients with certain underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by such vasodilatory effects.

In patients who are taking alpha$_1$ blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients. Therefore, the combination of Yuvanci and doxazosin is not recommended.

In the double-blind portion of the A DUE study, cardiac failure events (n=4) were reported within one month of treatment initiation with Yuvanci in patients over 65 years of age not previously treated with PAH-specific medicinal products. Two cases out of four resolved while on treatment, whereas the other two were discontinued due to other adverse events [a newly established diagnosis of Pulmonary Veno-Occlusive Disease (exclusionary as per study protocol) and anaemia].

Excipients with known effect

Yuvanci contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Effects of other medicinal products on Yuvanci

Strong CYP3A4 inducers
Potent inducers of CYP3A4 including rifampicin, St. John's wort, carbamazepine, and phenytoin may reduce the efficacy of Yuvanci. The concomitant use of Yuvanci should be avoided.

Rifampicin (600 mg daily) reduced the steady-state exposure to macitentan by 79% but did not affect the exposure to the active metabolite.

Rifampicin (600 mg daily), reduced tadalafil AUC by 88% and C_{max} by 46%, relative to the AUC and C_{max} values for tadalafil alone (10 mg).

Strong CYP3A4 inhibitors
The combination of Yuvanci with strong CYP3A4 inhibitors such as itraconazole, ketoconazole, voriconazole, clarithromycin, telithromycin, nefazodone, ritonavir and saquinavir is not recommended.

Ketoconazole (400 mg once daily) increased exposure to macitentan approximately 2-fold. Exposure to the active metabolite of macitentan was reduced by 26%.

Ketoconazole (200 mg daily), increased tadalafil (10 mg) single dose exposure (AUC) 2-fold and C_{max} by 15%, relative to the AUC and C_{max} values for tadalafil alone.

Ketoconazole (400 mg daily) increased tadalafil (20 mg) single dose exposure (AUC) 4-fold and C_{max} by 22%.

Ritonavir (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) single dose exposure (AUC) 2-fold with no change in C_{max}.

Ritonavir (500 mg or 600 mg twice daily) increased tadalafil (20 mg) single-dose exposure (AUC) by 32% and decreased C_{max} by 30%.

Dual moderate CYP3A4 and CYP2C9 inhibitors
Caution should be exercised when Yuvanci is administered concomitantly with moderate dual inhibitors of CYP3A4 and CYP2C9 (e.g., fluconazole and amiodarone).

Fluconazole 400 mg daily, a moderate dual inhibitor of CYP3A4 and CYP2C9, may increase exposure to macitentan approximately 3.8-fold, based on physiologically-based pharmacokinetic (PBPK) modelling. However, there was no clinically relevant change in exposure to the active metabolite of macitentan. The uncertainties of such modelling should be considered.

Co-administration of moderate CYP3A4 inhibitors with moderate CYP2C9 inhibitors
Moderate CYP3A4 inhibitor (e.g., ciprofloxacin, cyclosporine, diltiazem, erythromycin, verapamil) and moderate CYP2C9 inhibitor (e.g., miconazole and piperine) should be administered with caution if administered concomitantly with Yuvanci.

Co-administration of moderate CYP3A inhibitors
Cyclosporine A (100 mg twice daily) a combined CYP3A4 and OATP inhibitor, did not alter the steady-state exposure to macitentan and its active metabolite to a clinically relevant extent in *in vivo* studies.

Effects of Yuvanci on other medicinal products

Oral contraceptive pill
In *in vivo* studies, macitentan 10 mg once daily did not affect the pharmacokinetics of an oral contraceptive (norethisterone 1 mg and ethinyl estradiol 35 µg). At steady-state, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26% and C_{max} by 70% relative to oral contraceptive administered with placebo. There was no statistically significant effect of tadalafil on levonorgestrel which suggests the effect on ethinylestradiol is due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain, however, reliable contraception is mandatory for users of Yuvanci (see section 4.6).

Terbutaline
A similar increase in AUC and C_{max} seen with ethinylestradiol may be expected with oral administration of terbutaline, probably due to inhibition of gut sulphation by tadalafil. The clinical relevance of this finding is uncertain.

CYP1A2 substrates (e.g., theophylline)
When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 beats per minute) increase in heart rate.

CYP2C9 substrates (e.g., R-warfarin)
Macitentan given as multiple doses of 10 mg once daily had no effect on exposure to S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate) after a single dose of 25 mg warfarin. The pharmacodynamic effect of warfarin on International Normalised Ratio (INR) was not affected by macitentan. The pharmacokinetics of macitentan and its active metabolite were not affected by warfarin. Tadalafil (10 and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin , nor did tadalafil affect changes in prothrombin time induced by warfarin and did not potentiate the increase in bleeding time caused by acetyl salicylic acid.

P-glycoprotein substrates (e.g., digoxin)
Tadalafil (40 mg once per day) had no clinically significant effect on the pharmacokinetics of digoxin (P-gp substrate).

Breast cancer resistance protein (BCRP) substrate drugs:
In *in vivo* studies, macitentan 10 mg once daily did not affect the pharmacokinetics of a BCRP substrate drug (riociguat 1 mg; rosuvastatin 10 mg).

Pharmacodynamic interactions

Nitrates

In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, administration of Yuvanci to patients who are using any form of organic nitrate, such as nitroglycerin, isosorbide and amyl nitrate, is contraindicated (see section 4.3).

Riociguat

In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including tadalafil, is contraindicated (see section 4.3).

Anti-hypertensives (including Calcium channel blockers)

The co-administration of doxazosin (4 and 8 mg daily) and tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. Therefore, this combination is not recommended.
In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin.

In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of doxazosin -see above) is, in general, minor and not likely to be clinically relevant.

Alcohol

Alcohol concentrations were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen after co-administration with alcohol. Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 ml of 40% alcohol [vodka] in an 80 kg male), but in some subjects, postural dizziness and orthostatic hypotension were observed. Patients should be made aware of these potential side effects. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

Prostacyclin and its analogues such as epoprostenol or iloprost

The efficacy and safety of Yuvanci co-administered with prostacyclin or its analogues has not been studied in controlled clinical studies. Therefore, caution is recommended in case of co-administration.

Treatments for erectile dysfunction

The safety and efficacy of combinations of tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Patients should be informed not to take Yuvanci with these medicinal products.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Yuvanci treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified, appropriate advice on contraception provided, and reliable contraception is practised (see sections 4.3 and 4.4). Women should not become pregnant for 1 month after

discontinuation of Yuvanci. Monthly pregnancy tests during treatment with Yuvanci are recommended to allow the early detection of pregnancy.

Yuvanci is contraindicated in women of childbearing potential who are not using reliable contraception (see section 4.3).

Pregnancy

There are no data from the use of Yuvanci in pregnant women.

There are no data from the use of macitentan in pregnant women. Studies with macitentan in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is still unknown.

There are limited data from the use of tadalafil in pregnant women.

Yuvanci is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is unknown whether active substances of Yuvanci are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of macitentan in milk. A risk to the breastfed child cannot be excluded.

Yuvanci is contraindicated during breastfeeding (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals was observed after treatment with macitentan (see section 5.3). Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse impact on spermatogenesis in men.

Two clinical studies with tadalafil suggested no impairment of fertility in humans, although a decrease in sperm concentration was seen in some men.

4.7 Effects on ability to drive and use machines

Yuvanci has minor influence on the ability to drive and use machines. However, undesirable effects may occur (e.g., headache, hypotension) that may influence the ability to drive and use machines (see section 4.8). Patients should be aware of how they react to Yuvanci, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (occurring in the Yuvanci treated patients) from the combined double-blind / open-label A DUE study data were anaemia/haemoglobin decrease (22.2%), oedema/fluid retention (17.3%), and headache (14.1%). In this study, the most common serious adverse event was anaemia (1.1% or 2 patients), followed by palpitations, hypotension, intermenstrual bleeding, oedema/fluid retention and influenza, each reported in 1 patient (0.5%)

Tabulated list of adverse reactions

The safety profile presented below is based on data for Yuvanci and the known safety profile of the individual components macitentan and tadalafil.

The safety data for Yuvanci was obtained from a double-blind, active controlled, Phase 3 clinical study (A DUE) and an open-label extension in patients with PAH. The total number of patients receiving Yuvanci was 185 patients with a median exposure to Yuvanci of 59.9 weeks.

Known adverse reactions for macitentan and tadalafil which have not been observed in the A DUE study, are included in table 1 based on the prescribing information for the individual components macitentan and tadalafil.

Adverse reactions are listed by MedDRA system organ class and by frequency. Frequency categories are defined as follows: 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); and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions in patients with PAH treated with Yuvanci, macitentan and/or tadalafil

System organ class	Adverse reaction(s)	Frequency[a]
Infections and infestations	Bronchitis[b]	Very common
	Influenza	Common
	Urinary tract infection	Common
	Upper respiratory tract infection	Common
	Pharyngitis[b]	Common
Blood and lymphatic system disorders	Anaemia/ Haemoglobin decrease[c]	Very common
	Leukopenia	Common
	Thrombocytopenia[a]	Common
Immune system disorders	Hypersensitivity[a] (including Pruritus[d])	Common
	Angioedema[a]	Common
Nervous system disorders	Headache	Very common
	Syncope	Very common
	Migraine[a]	Common
	Seizure[e]	Uncommon
	Transient amnesia[e]	Uncommon
	Stroke[e] (including haemorrhagic events)	Not known[f]
Eye disorders	Vision blurred	Common
	Non-arteritic anterior ischaemic optic neuropathy (NAION)[e]	Not known[f]
	Retinal vascular occlusion[e]	Not known[f]
	Visual field defect[e]	Not known[f]
	Central serous chorioretinopathy[e]	Not known[f]
Ear and labyrinth disorders	Tinnitus[e]	Uncommon
	Sudden hearing loss[e]	Not known[f]
Cardiac disorders	Palpitations	Common
	Tachycardia[a]	Common
	Sudden cardiac death[e]	Uncommon
	Myocardial infarction[e]	Not known[f]
	Unstable angina pectoris[e]	Not known[f]
	Ventricular arrhythmia[e]	Not known[f]
Vascular disorders	Flushing[a,g]	Very common
	Hypotension	Common

Respiratory, thoracic and mediastinal disorders	Nasopharyngitis[a] (including nasal congestion, sinus congestion and rhinitis)	Very common
	Epistaxis	Common
Gastrointestinal disorders	Nausea[a]	Very common
	Dyspepsia[a]	Very common
	Abdominal discomfort[a]	Very common
	Abdominal pain[a]	Very common
	Vomiting	Common
	Gastroesophageal reflux disease	Common
Hepatobiliary disorders	Transaminases increased	Common
Skin and subcutaneous tissue disorders	Rash	Common
	Urticaria[e]	Uncommon
	Hyperhidrosis[e]	Uncommon
	Stevens-Johnson syndrome[e]	Not known[f]
	Exfoliative dermatitis[e]	Not known[f]
Musculoskeletal and connective tissue disorders	Myalgia[a]	Very common
	Back pain[a]	Very common
	Pain in extremity[a]	Very common
Renal and urinary disorders	Haematuria[e]	Uncommon
Reproductive system and breast disorders	Increased uterine bleeding[h]	Common
	Priapism[e]	Uncommon
	Penile haemorrhage[e]	Uncommon
	Haematospermia[e]	Uncommon
	Prolonged erections[e]	Not known[f]
General disorders and administration site conditions	Oedema[i]	Very common
	Fluid retention[i]	Very common
	Swelling face	Common
	Chest pain	Common

[a] When the same adverse reaction has been observed in more than one medicinal product (i.e., macitentan, tadalafil, and Yuvanci), the category representing the highest frequency is presented.
[b] Not observed with Yuvanci in double-blind study data, but reported with macitentan monotherapy
[c] Includes anaemia, iron deficiency anaemia, anaemia of chronic disease, haemoglobin decreased, normochromic anaemia, pancytopenia, blood loss anaemia, and myelofibrosis.
[d] Pruritus was observed with macitentan with a frequency of uncommon.
[e] Not observed with Yuvanci in double-blind study data, but reported with tadalafil monotherapy.
[f] Events not reported in registration studies and cannot be estimated from the available data. The adverse reactions have been included in the table as a result of postmarketing or clinical study data from the use of tadalafil in the treatment of erectile dysfunction.
[g] Includes flushing and hot flush.
[h] Includes heavy menstrual bleeding, intermenstrual bleeding, polymenorrhagia, and vaginal haemorrhage. Frequency based on exposure in females.
[i] Includes oedema peripheral, peripheral swelling, generalised oedema, swelling, bone marrow oedema, fluid retention, joint swelling, oedema, hypervolaemia, and pericardial effusion.

Description of selected adverse reactions

Hypotension

Hypotension has been associated with the use of ERAs including macitentan. In the double-blind period of the A DUE study with Yuvanci in patients with PAH, the incidence of hypotension was 7.5% in the Yuvanci arm; there were no hypotension events reported in the macitentan and tadalafil monotherapy arms. The incidence of hypotension for Yuvanci in the combined double-blind / open-label study was 6.5%.

In SERAPHIN, a long-term double-blind study of macitentan in patients with PAH, hypotension was reported for 7.0% and 4.4% of patients on macitentan 10 mg monotherapy and placebo arms, respectively.

Oedema/fluid retention

Oedema/fluid retention has been associated with the use of ERAs including macitentan. In the double-blind period of the A DUE study with Yuvanci in patients with PAH, the incidence of Oedema/fluid retention was 20.6%, 14.3% and 15.9% in the Yuvanci , macitentan and tadalafil arms, respectively. The incidence of oedema/fluid retention for Yuvanci in the combined double-blind / open-label phase was 17.3%.

In SERAPHIN, the incidence of oedema adverse events in the macitentan 10 mg monotherapy and placebo treatment arms was 21.9% and 20.5%, respectively.

Laboratory abnormalities

Liver aminotransferases
In the double-blind period of the A DUE study with Yuvanci in patients with PAH the incidence of elevated aminotransferase ≥ 3 × ULN was 1.0% and 4.5% in Yuvanci and tadalafil arms, respectively. No elevation of aminotransferase ≥ 3 × ULN was reported in macitentan arm. The incidence of elevated aminotransferases ≥ 3 × ULN was 3.4% and the incidence of elevated aminotransferases ≥ 8 × ULN was 1.1% for Yuvanci in combined double-blind / open-label phase.

In SERAPHIN, the incidence of aminotransferase elevations (ALT/AST) > 3 × ULN was 3.4% on macitentan 10 mg monotherapy and 4.5% on placebo. Elevations > 5 × ULN occurred in 2.5% of patients on macitentan 10 mg monotherapy versus 2% of patients on placebo.

Haemoglobin decreases and anaemia
In the double-blind period of the A DUE study with Yuvanci in patients with PAH, the incidence of anaemia was 18.7%, 2.9%, and 2.3% in Yuvanci, macitentan and tadalafil arms, respectively. The mean decrease from baseline in haemoglobin concentration at week 16 was greater in magnitude for Yuvanci compared with macitentan and tadalafil: 1.39 g/dL (0.87 mmol/L), 0.68 g/dL (0.42 mmol/L) and 0.08 g/dL (0.05 mmol/L) in the Yuvanci, macitentan and tadalafil arms, respectively. In the combined double-blind / open-label phase of the study, treatment with Yuvanci was associated with a decrease in mean haemoglobin concentration of 0.95 g/dL (0.59 mmol/L) from baseline to week 47 (106 patients).

In SERAPHIN, macitentan 10 mg monotherapy was associated with a mean decrease in haemoglobin of 1 g/dL (0.69 mmol/L) versus placebo

White blood cells
In the double-blind period of the A DUE study with Yuvanci in patients with PAH, the mean decrease from baseline in leukocytes at week 16 was greater in the Yuvanci compared with macitentan and tadalafil: 1.4 × 10^9/L in the Yuvanci and 0.5 × 10^9/L in macitentan and tadalafil arms. In the combined double-blind / open-label phase of the study, treatment with Yuvanci was associated with a decrease in mean leukocyte count of 1.2 × 10^9/L from baseline to week 47 (106 patients).

In SERAPHIN, macitentan 10 mg monotherapy was associated with a decrease in mean leucocyte count from baseline of 0.7 × 10^9/L versus no change in placebo-treated patients.

Platelets
In the double-blind period of the A DUE study with Yuvanci in patients with PAH, the mean decrease from baseline in platelets at week 16 was in the Yuvanci arm was 16.2 × 10^9/L compared with 19.3 × 10^9/L and 5.6 × 10^9/L in macitentan and tadalafil arms, respectively. In the combined double-blind / open-label phase of the study, treatment with Yuvanci was associated with a decrease in mean platelet count of 16.6 × 10^9/L from baseline to week 47 (104 patients).

In SERAPHIN, macitentan 10 mg monotherapy was associated with a decrease in mean platelet count from baseline of 17 × 10^9/L, versus a mean decrease of 11 × 10^9/L in placebo-treated patients, respectively.

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

Macitentan has been administered as a single dose of up to 600 mg to healthy subjects. Adverse reactions of headache, nausea, and vomiting were observed. Tadalafil has been administered as a single dose of up to 500 mg to healthy subjects. Adverse reactions were similar to those seen at lower doses. Based on the individual component data, dialysis is unlikely to be effective. In the event of an overdose, standard supportive measures must be taken, as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-hypertensives, anti-hypertensives for pulmonary arterial hypertension
ATC code: C02KX54.

Mechanism of action

Yuvanci is a single tablet combination therapy that contains two oral components with different mechanisms of action to improve pulmonary arterial hypertension: macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 inhibitor (PDE5i).

Macitentan is an orally active potent endothelin (ET) receptor antagonist, active on both ET_A and ET_B receptors and approximately 100-fold more selective for ET_A as compared to ET_B *in vitro*. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. ET-1 and its receptors (ET_A and ET_B) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage.

Tadalafil is a potent and selective inhibitor of PDE5, the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Clinical efficacy and safety

The efficacy of Yuvanci was demonstrated in a multi-national, multi-centre, double-blind, adaptive, randomised, active-controlled, parallel-group study (A DUE) in 187 patients with PAH (WHO FC II–III). The study was designed to compare the efficacy and safety of Yuvanci to each monotherapy, macitentan or tadalafil. Patients with pulmonary vascular resistance (PVR) of at least 240 dyn×s/cm^5

were randomised to receive Yuvanci (macitentan 10 mg and tadalafil 40 mg) (n=108), 10 mg macitentan monotherapy (n=35) or 40 mg tadalafil monotherapy (n=44), once daily.

Patients who were not on a therapeutic PDE-5i dose at baseline, received a 1-week titration period of macitentan 10 mg and tadalafil 20 mg.

Patients who received treatment during the double-blind treatment period (n=186) were either treatment-naïve (52.7%) to any PAH specific monotherapy, or on an ERA (17.2%), or a PDE5i (30.1%). Patients enrolled had idiopathic PAH (50.5%), heritable PAH (4.8%), PAH associated with connective tissue disease (34.9%), or PAH associated with congenital heart disease (3.2%). The mean age was 50.2 years (range 18–80), 20.4% of patients were ≥ 65 years of age, 22% were male and 61.8% were white. At the time of enrollment, 51.1% of patients were WHO FC II and 48.9% were WHO FC III.

The primary endpoint of the study was change in PVR expressed as the ratio of Week 16 to baseline in patients with PAH, for the comparison of Yuvanci versus the individual monotherapies.

The key secondary endpoint was change in mean 6-minute walk distance (6MWD) from baseline to 16 weeks of therapy in patients with PAH, for the comparison of Yuvanci versus the individual monotherapies.

Haemodynamics

Treatment with Yuvanci resulted in a statistically significant effect of 0.71 (95% CI 0.61, 0.82, $p < 0.0001$) representing a 29% reduction in PVR as compared to macitentan, and of 0.72 (95% CI 0.64, 0.80, $p < 0.0001$) representing a 28% reduction in PVR as compared to tadalafil (Table 2). Consistent efficacy of Yuvanci on the primary endpoint was seen across subgroups of age, sex, race, and baseline WHO FC. Additionally, consistent efficacy was observed in patients who were either treatment-naïve, or previously exposed to an ERA or PDE5i.

Table 2: Change in PVR from baseline to week 16 of treatment

	Treatment-naïve and prior ERA treatment		**Treatment-naïve and prior PDE-5i treatment**	
	Macitentan (n=35)	**Yuvanci (n=70)**	**Tadalafil (n=44)**	**Yuvanci (n=86)**
Baseline mean PVR (95% CI)	816 (683, 949)	834 (687, 982)	802 (639, 965)	885 (749, 1020)
Reduction in mean PVR at Week 16 (dyn×s/cm^5) (95% CI)	-162 (-242, -82)	-371 (-471, -270)	-181 (-251, -111)	-385 (-468, -301)
Geometric mean PVR (Week 16/ Baseline) (95% CI)	0.77 (0.69, 0.87)	0.55 (0.50, 0.60)	0.78 (0.72, 0.84)	0.56 (0.52, 0.60)
Geometric mean ratios (95% CI)		0.71 (0.61, 0.82)		0.72 (0.64, 0.80)
2-sided p-value		<.0001		<.0001

PVR=pulmonary vascular resistance; CI= confidence intervals; n=number of patients.

Exercise capacity

A numerical increase in 6MWD of Yuvanci compared to either macitentan or tadalafil was observed (table 3).

Table 3: Change in mean 6MWD from baseline to week 16 of treatment

	Treatment-naïve and prior ERA treatment		Treatment-naïve and prior PDE-5i treatment	
	Macitentan (n=35)	**Yuvanci (n=70)**	**Tadalafil (n=44)**	**Yuvanci (n=86)**
Baseline mean (95% CI)	347 (318, 377)	354 (330, 379)	362 (341, 383)	351 (330, 372)
Change from baseline at Week 16 (m) mean (95% CI)	39 (15, 62)	53 (32, 74)	16 (3, 29)	43 (27, 60)
Mean differences (95% CI)		16 (-17, 49)		25 (-0.9, 52)
2-sided p-value		0.38		0.06

CI=confidence intervals;6MWD) 6-minute walk distance; n= number of patients

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Yuvanci in all subsets of the paediatric population in PAH (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The bioavailability of macitentan and tadalafil administered as Yuvanci was comparable to when macitentan 10 mg and tadalafil 40 mg were co-administered separately; bioequivalence was established following single-dose administration in healthy subjects. Bioequivalence of Yuvanci (10 mg macitentan / 20 mg tadalafil) was also established for the 10 mg macitentan and 20 mg tadalafil individual components.

Absorption

When Yuvanci (10 mg macitentan/40 mg tadalafil) tablet was administered to healthy subjects with a high-fat meal, no effect of food on the pharmacokinetics of macitentan was observed and the AUC for tadalafil remained unchanged, while C_{max} increased by 45%. This increase in C_{max} of tadalafil is not considered clinically significant.

No clinically significant differences in the pharmacokinetics of macitentan 10 mg and tadalafil 20 mg were observed following administration of Yuvanci (macitentan 10 mg and tadalafil 20 mg) tablet to healthy subjects following a high-fat, high calorie meal.

Macitentan

Maximum plasma concentrations of macitentan are achieved about 9 hours after administration.

Tadalafil

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) is achieved at a median time of about 2 hours after dosing. Absolute bioavailability of tadalafil following oral dosing has not been determined.

Distribution

Macitentan

Macitentan and its active metabolite are highly bound to plasma proteins (> 99%), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein. Macitentan and its active metabolite ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for macitentan and ACT-132577, respectively.

Tadalafil

The mean volume of distribution is approximately 77 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.
Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Macitentan

Macitentan has four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This reaction is dependent on the cytochrome P450 system (CYP), mainly CYP3A4 (approximately 99%) with minor contributions of CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to the pharmacological effect. Other metabolic pathways yield products without pharmacological activity. For these pathways, CYP2C9 plays a predominant role with minor contributions from CYP2C8, CYP2C19 and CYP3A4.

Tadalafil

Tadalafil is predominantly metabolised by the CYP3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13 000-fold less potent than tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination

Macitentan

Plasma concentrations of macitentan and its active metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively. Macitentan is only excreted after extensive metabolism. The major excretion route is via urine, accounting for about 50% of the dose.

Tadalafil

The mean oral clearance for tadalafil is 3.4 l/h and the mean half-life is 24 hours in healthy subjects.

Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).

Linearity/non-linearity

Macitentan

After repeated administration, the pharmacokinetics of macitentan are dose-proportional up to and including 30 mg.

Tadalafil

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 mg to 40 mg, a less than proportional increase in exposure is observed. During tadalafil 20 mg and 40 mg once daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.5-fold of that after a single dose.

Pharmacokinetic interaction studies

At their clinical doses, macitentan and tadalafil have no known effect on CYP450 isoforms or transporters.

Macitentan or tadalafil as a substrate of drug transporters:

Macitentan is not a substrate for P-gp/MDR-1. Macitentan and its active metabolite are not relevant substrates of OATP1B1 and OATP1B3 but enter the liver by passive diffusion. Tadalafil is a substrate of P-gp.

Special populations

Renal impairment

The pharmacokinetics of Yuvanci has not been studied in patients with renal impairment.

Exposure to macitentan and its active metabolite was increased by 1.3-and 1.6-fold, respectively, in patients with severe renal impairment. This increase is not considered clinically relevant for macitentan monotherapy.

In clinical pharmacology studies using single-dose tadalafil (5 to 20 mg), tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 ml/min) or moderate (creatinine clearance 31 to 50 ml/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, C_{max} was 41% higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Yuvanci is not recommended in patients undergoing dialysis or in patients with severe renal impairment (creatinine clearance <30 ml/min). due to increased tadalafil exposure (AUC), lack of clinical experience and the lack of ability to influence clearance by dialysis (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of Yuvanci has not been studied in patients with hepatic impairment.

Exposure to macitentan was decreased by 21%, 34%, and 6% and, for the active metabolite by 20%, 25%, and 25% in subjects with mild, moderate or severe hepatic impairment, respectively. This decrease is not considered clinically relevant for macitentan monotherapy.

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There are limited clinical data on the safety of tadalafil in patients with severe hepatic insufficiency (Child-Pugh Class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment.

Patients with PAH

Exposure to macitentan and its active metabolite in patients with PAH was approximately 1.2-fold, and 1.3-fold higher than in healthy subjects, respectively.

Exposure to tadalafil in patients with PAH was 1.3-fold greater than in healthy subjects. These differences are not considered clinically relevant.

No clinically relevant effects on the pharmacokinetics of macitentan and tadalafil are observed in elderly or due to race or gender.
No clinically relevant effects on the pharmacokinetics of tadalafil are observed in patients with diabetes.

5.3 Preclinical safety data

Non-clinical studies with Yuvanci have not been performed. The nonclinical toxicology data are based on findings in studies with macitentan and tadalafil individually.

Macitentan

Intimal thickening of coronary arteries was observed in dogs at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

Macitentan was not genotoxic in a standard battery of *in vitro* and *in vivo* assays. Macitentan was not phototoxic *in vivo* after single dose at exposures of up to 24-fold the human exposure. Carcinogenicity studies of 2 years' duration did not reveal a carcinogenic potential at exposures 18-fold and 116-fold the human exposure in rats and mice, respectively.

Testicular tubular dilatation was observed in chronic toxicity studies with male rats and dogs with safety margins of 11.6 and 5.8, respectively. Tubular dilatation was fully reversible. After 2 years of treatment, testicular tubular atrophy was seen in rats at 4-fold the human exposure. Hypospermatogenesis was observed in the life-long carcinogenicity study in rats and in the repeat-dose toxicity studies in dogs at exposures that provide safety margins of 9.7 in rats and 23 in dogs. The safety margins for fertility were 18 for male and 44 for female rats.

Macitentan was teratogenic in rabbits and rats at all doses tested. In both species there were cardiovascular and mandibular arch fusion abnormalities.

Administration of macitentan to female rats from late pregnancy through lactation at maternal exposures 5-fold the human exposure, caused reduced pup survival and impairment of the reproductive capability of the offspring, which was exposed to macitentan during late intrauterine life and via the milk during the suckling period.

Treatment of juvenile rats from postnatal day 4 to day 114 caused reduced body weight gain leading to secondary effects on development (delay of descensus testis, reversible reduction of long-bone length, prolonged oestrous cycle). Increased pre- and post-implantation loss, decreased mean number of pups, and decreased testis and epididymis weights, were observed at exposures 7-fold the human exposure. Testicular tubular atrophy, and effects on reproductive variables and sperm morphology were recorded at exposures 3.8-fold the human exposure.

Tadalafil

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose (E463a)
Lactose monohydrate
Magnesium stearate (E470b)
Microcrystalline cellulose (E460i)
Polysorbate 80 (E433)
Povidone (E1201)
Sodium starch glycolate
Sodium lauryl sulfate

Yuvanci 10 mg/20 mg film-coat

Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Lactose monohydrate
Talc (E553b)
Titanium dioxide (E171)
Triacetin (E1518)

Yuvanci 10 mg/40 mg film-coat

Hypromellose
Lactose monohydrate
Talc (E553b)
Titanium dioxide (E171)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Yuvanci 10 mg/20 mg film-coated tablets

30 × 1 film-coated tablets in aluminium perforated unit-dose blisters with integrated desiccant. The product contact layer is a polyethylene layer without desiccant.

Yuvanci 10 mg/40 mg film-coated tablets

30 × 1 film-coated tablets in aluminium perforated unit-dose blisters with integrated desiccant. The product contact layer is a polyethylene layer without desiccant.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/24/1859/001
EU/1/24/1859/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: XXXX

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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 (MAH) shall submit the first PSUR 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 marketing authorisation holder (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.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Yuvanci is marketed, all patients who are expected to use Yuvanci are provided with the following educational material:

- Patient Card.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Yuvanci 10 mg/20 mg film-coated tablets
macitentan/tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg macitentan and 20 mg tadalafil.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before 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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original package in order to protect from moisture.

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/24/1859/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yuvanci 10 mg/20 mg

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

Yuvanci 10 mg/20 mg film-coated tablets
macitentan/tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag Int

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Yuvanci 10 mg/40 mg film-coated tablets
macitentan/tadalafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg macitentan and 40 mg tadalafil.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
30 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before 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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original package in order to protect from moisture.

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

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/24/1859/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Yuvanci 10 mg/40 mg

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

Yuvanci 10 mg/40 mg film-coated tablets
macitentan/tadalafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag Int

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Patient Card

Page 1

For the treatment of pulmonary arterial hypertension

This card contains important safety information you need to be aware of when receiving treatment with Yuvanci. Carry this card with you at all times and show it to any doctor involved in your medical care.

Yuvanci® 10 mg/20 mg
Yuvanci® 10 mg/40 mg
macitentan/tadalafil
film-coated tablets

EN

Page 2

It is important that you report immediately to your prescribing doctor pregnancy or any side effects that may occur during treatment with Yuvanci.

Treatment centre:

Name of prescribing doctor:

Phone number of prescribing doctor:

Page 3

Pregnancy
Yuvanci may harm the development of the foetus. Therefore you must not take Yuvanci if you are pregnant and you must also not become pregnant while taking Yuvanci. Moreover, if you are suffering from pulmonary arterial hypertension, the occurrence of a pregnancy can severely deteriorate the symptoms of your disease.

Page 4

Contraception
You need to use a reliable form of birth control (contraception) while you are taking Yuvanci. Be sure to discuss any questions you may have with your doctor.

You should have a pregnancy test before initiation of Yuvanci and every month during treatment even if you think that you are not pregnant.

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Like other medicines of this class, Yuvanci can have effects on the liver. Your doctor will take blood test before you start treatment with Yuvanci and during treatment to test whether your liver is working properly.

Signs that your liver may not be working properly include:
- nausea (urge to vomit)
- vomiting
- fever (high temperature)
- pain in your stomach (abdomen)
- jaundice (yellowing of your skin or the whites of your eyes)
- dark-coloured urine
- itching of your skin
- lethargy or fatigue (unusual tiredness or exhaustion)
- flu-like syndrome (joint and muscle pain with fever)

Page 6

If you notice any of these signs, tell your doctor immediately. If you have any question about your treatment, ask your doctor or pharmacist.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Yuvanci 10 mg/20 mg film-coated tablets
Yuvanci 10 mg/40 mg film-coated tablets
macitentan/tadalafil

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.
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yuvanci is and what it is used for

Yuvanci contains two active substances, macitentan and tadalafil. Macitentan belongs to a class of medicines called endothelin receptor antagonists (ERAs). Tadalafil belongs to a class of medicines called phosphodiesterase type 5 inhibitors (PDE5i).

Yuvanci is used in adults for the long-term treatment of World Health Organization (WHO) Class II or Class III pulmonary arterial hypertension (PAH). It is used as an alternative to taking both macitentan and tadalafil as single tablets.

PAH is high blood pressure in the blood vessels that carry blood from the heart to the lungs (the pulmonary arteries). In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy, and short of breath. The class reflects the seriousness of the disease: patients with Class II PAH have slight limitation of physical activity and those with Class III disease have marked limitation of physical activity.

Yuvanci widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure, relieves the symptoms and results in an improved ability to do physical activity and improves the course of the disease.

2. What you need to know before you take Yuvanci

Do not take Yuvanci if you:

- are allergic to macitentan, tadalafil, or any of the other ingredients of this medicine (listed in section 6).
- have had a heart attack within the last 90 days.
- are pregnant or if you could become pregnant because you are not using reliable birth control (contraception). See section 2 ‘Pregnancy and breastfeeding’.
- are breastfeeding. See section 2 ‘Pregnancy and breastfeeding’.

- have severe liver disease or if you have very high levels of liver enzymes in your blood. Talk to your doctor, who will decide whether this medicine is suitable for you.
- have very low blood pressure (90/50 mmHg).
- are taking nitrates or riociguat. See section 2 'Other medicines and Yuvanci'
- have ever had non-arteritic anterior ischaemic optic neuropathy (NAION, a condition also described as "stroke of the eye"), a loss of vision due to reduced blood flow to the eye.

If any of these apply to you, please **tell your doctor**.

Warnings and precautions

<u>You will need laboratory tests before using Yuvanci and during treatment, as indicated by your doctor</u>:

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Yuvanci and regularly (once a month) during treatment. See section 2 'Pregnancy and breastfeeding'.

Your doctor will take blood to test:
- whether your liver is working properly
- whether you have anaemia (a reduced number of red blood cells)

Yuvanci may cause increases in liver enzymes (proteins), which may be a sign that your liver is not working properly. Other signs that your liver may not be working properly include the following symptoms:
- feeling sick (nausea)
- vomiting
- fever
- pain in your stomach (abdomen)
- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin
- unusual tiredness or exhaustion (lethargy or fatigue)
- flu-like syndrome (joint and muscle pain with fever)

If you notice any of these signs during treatment with Yuvanci, **tell your doctor immediately**.

Yuvanci may cause anaemia (low levels of red blood cells). If you develop any of the following, which may be symptoms of anaemia, **tell your doctor**:
- dizziness
- tiredness
- feeling generally unwell
- weakness
- fast heart rate,
- palpitations (a forceful heartbeat that may be rapid or irregular)
- pallor

<u>Before taking the tablets, tell your doctor if you have</u>
- any cardiovascular (having to do with the heart and blood vessels) conditions other than your pulmonary hypertension including:
    - aortic and mitral valve disease (problems with the valves in the heart that can affect blood flow)
    - pericardial constriction (a condition where the pericardium, the sac around the heart, becomes tight, affecting the heart's ability to function correctly)

    - restrictive or congestive cardiomyopathy (a condition where the heart muscle becomes stiff or weak, leading to problems in pumping blood effectively)
    - left ventricular dysfunction (a condition where the left side of the heart has difficulty in pumping blood efficiently to the rest of the body)
    - arrhythmias (abnormal heart rhythms)
    - coronary artery disease (heart disease caused by narrowing or blockage of blood vessels supplying the heart muscle)
    - uncontrolled hypertension (high blood pressure that is not adequately controlled)
- problems with your blood pressure such as significant decreases in blood pressure when standing up or when blood pressure is consistently lower than normal
- any inherited disease that causes damage to the retina (the light sensitive membrane at the back of the eye)
- a severe liver problem
- a severe kidney problem

If you have kidney problems, talk to your doctor before using Yuvanci. You may have a higher risk of experiencing low blood pressure and anaemia during treatment with Yuvanci.

In patients with pulmonary veno-occlusive disease (obstruction of the lung veins), the use of medicines for treatment of PAH, including Yuvanci, may lead to pulmonary oedema (build up of fluid in the lungs). **Tell your doctor immediately** if you have signs of pulmonary oedema when using Yuvanci, such as

- a sudden, important increase in breathlessness
- coughing
- tiredness after exertion
- difficulty breathing while lying flat

Before taking Yuvanci, **tell your doctor** if you have any deformation of the penis such as:

- angulation, a condition where the penis becomes curved, possibly due to cavernosal fibrosis (scarring of certain tissues in the penis).
- Peyronie's disease, a condition in adult men, where they have a 'plaque' of scar tissue that can be felt, accompanied by a curve to their penis.
- or a condition that may predispose you to priapism (a prolonged and an painful erection which may occur without sexual stimulation) such as an abnormality of red blood cells (sickle cell anaemia), cancer of the bone marrow (multiple myeloma) or cancer of the blood cells (leukaemia).

If during treatment with Yuvanci, you experience an erection lasting 4 hours or more, **seek immediate medical assistance.**

Visual defects and sudden loss of vision have occurred while using tadalafil and PDE5 inhibitors. If you experience sudden decrease or loss of vision or your vision is distorted or dimmed, during treatment stop taking Yuvanci and **contact your doctor immediately.**

Decreased or sudden hearing loss has been noted in some patients taking tadalafil. Although it is not known if the event is directly related to tadalafil, if you experience decreased or sudden hearing loss, **contact your doctor immediately.**

Children and adolescents

Do not give this medicine to children and adolescents below 18 years because Yuvanci has not been tested in children.

Other medicines and Yuvanci

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Yuvanci if you are taking any of the following medicines:
- riociguat (a medicine used to treat PAH and chronic thromboembolic pulmonary hypertension)
- nitrates such as nitroglycerin, isosorbide and amyl nitrate (for chest pain)

Please talk to your doctor or pharmacist if you are taking any of the following medicines including:

Medicines that may decrease the effectiveness of Yuvanci by decreasing the amount of Yuvanci in the blood, including:
- St John's Wort (a herbal preparation used to treat depression)
- phenytoin or carbamazepine (medicines used to treat epilepsy)
- rifampicin (an antibiotic used to treat infections)

Medicines that may increase the risk of side effects of Yuvanci, including:
- clarithromycin, telithromycin, ciprofloxacin, erythromycin (antibiotics used to treat infections)
- ritonavir, saquinavir (used to treat HIV infections)
- doxazosin (used to treat high blood pressure or prostate problems)
- nefazodone (used to treat depression)
- ketoconazole (except when used in a shampoo), fluconazole, itraconazole, miconazole, voriconazole (medicines used against fungal infections)
- amiodarone (to control the heartbeat)
- cyclosporine (used to prevent organ rejection after transplant), diltiazem, verapamil (to treat high blood pressure or specific heart problems)
- prostacyclin similar medicines such as epoprostenol and iloprost (used to treat PAH, lung scarring and blocked arteries)

Yuvanci with food and alcohol
If you are taking piperine as a dietary supplement, this may alter how the body responds to some medicinal products, including Yuvanci. Please talk to your doctor or pharmacist should this be the case.

Drinking alcohol may temporarily lower your blood pressure. If you have taken or are planning to take Yuvanci, avoid excessive drinking (over 5 units of alcohol), since this may increase the risk of dizziness when standing up.

Pregnancy and breast-feeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Yuvanci must not be taken during pregnancy as it may harm unborn baby. See section 2 "Do not take Yuvanci if you".

- If it is possible that you could become pregnant, use a reliable form of birth control (contraception) while you are taking Yuvanci. Talk to your doctor about contraception.
- Do not take Yuvanci if you are pregnant or planning to become pregnant.
- If you become pregnant or think that you may be pregnant while you are taking Yuvanci, or shortly after stopping Yuvanci (up to 1 month), **see your doctor immediately.**

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Yuvanci and regularly (once a month) while you are taking Yuvanci.

It is not known if Yuvanci is transferred to breast milk. Do not breastfeed while you are taking Yuvanci. Talk to your doctor if you are planning to breastfeed. See section 2 “Do not take Yuvanci if you”

Fertility
Yuvanci may cause decreased sperm count in men. Talk to your doctor if you are planning to have children.

Driving and using machines
Yuvanci can cause side effects such as headaches and low blood pressure (listed in section 4), and the symptoms of pulmonary arterial hypertension can also make you less fit to drive. Check carefully how you react to the Yuvanci before driving or using any machinery.

Yuvanci contains lactose monohydrate and sodium
- Yuvanci contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
- This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Yuvanci

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

The recommended dose of Yuvanci is one 10 mg/40 mg tablet, once a day. In some situations your doctor may decide starting on a lower dose of 10 mg/20 mg dose once a day. It lets your body adjust to the new medicine. If tolerated, your doctor will then increase your dose to the dose of one 10 mg/40 mg tablet, once a day.

Swallow the whole tablet, with a glass of water. Do not chew or break the tablet. You can take Yuvanci with or without food. It is best to take the tablet at the same time each day.

If you take more Yuvanci than you should
Contact your doctor or pharmacist immediately. You may experience any of the side effects described in section 4.

If you forget to take Yuvanci
If you forget to take Yuvanci, take a dose as soon as you remember, then continue to take your tablets at the usual times. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Yuvanci
Yuvanci is a treatment that you will need to keep on taking to control your PAH. Do not stop taking Yuvanci unless you have agreed this with your doctor.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects listed below have been observed with Yuvanci or have been previously reported with the active substances (macitentan or tadalafil) in Yuvanci and may also occur with Yuvanci.

If you experience any of the following side effects stop using the medicine and seek medical help immediately:

- serious allergic reactions (may affect up to 1 in 10 people).
    - Symptoms include swelling around the eyes, face, lips, tongue or throat which can be life threatening if throat swelling blocks the airway. If you experience any of these symptoms during treatment with Yuvanci seek immediate medical assistance.
- chest pain (may affect up to 1 in 10 people).
    - if you experience chest pain during treatment with Yuvanci seek immediate medical assistance. Do not use nitrates to treat your symptoms.
- priapism, a prolonged and possibly painful erection which may occur without sexual stimulation (may affect up to 1 in 100 people).
    - If you experience an erection lasting more than 4 hours during treatment with Yuvanci, seek immediate medical assistance.
- sudden loss of vision or distorted, dimmed, blurred central vision or sudden decrease of vision. (It is not known how often people may be affected by these side effects).
    - If you experience these side effects during treatment with Yuvanci seek immediate medical assistance.

Other side effects include

Very common (may affect more than 1 in 10 people)
- Oedema/fluid retention (swelling), especially of the ankles and feet
- Headache
- Anaemia (low number of red blood cells) or reduced haemoglobin (the protein in red blood cells that carries oxygen around the body)
- Nausea (feeling sick)
- Dyspepsia (indigestion)
- Abdominal (belly) pain
- Abdominal discomfort
- Nasopharyngitis (inflammation of the throat and nose)
- Bronchitis (inflammation of the airways)
- Myalgia (muscle aches)
- Back pain
- Pain in the legs and arms
- Flushing (redness of the skin)

Common (may affect up to 1 in 10 people)
- Vomiting (being sick)
- Gastroesophageal reflux disease (acid reflux)
- Syncope (fainting)
- Migraine
- Influenza (flu)
- Urinary tract infection (infection of the parts of the body that collect and pass out urine)
- Respiratory tract infection (infection of the breathing system, infected chest or nose, sinuses or throat, a cold)
- Pharyngitis (inflammation of the throat)
- Epistaxis (nosebleed)
- Palpitations (a forceful heartbeat that may be rapid or irregular)
- Tachycardia (rapid heartbeat)
- Increased levels of liver enzymes, as shown in blood tests
- Leukopenia (low levels white blood cells)
- Thrombocytopenia (low blood levels of platelets, components that help the blood to clot)
- Hypotension (low blood pressure)
- Vision blurred (blurred vision)

- Increased uterine (relating to the womb) bleeding
- Rash
- Hypersensitivity (allergic reactions), including itching

Uncommon (may affect up to 1 in 100 people)
- Seizure
- Transient amnesia (passing memory loss)
- Sudden cardiac death (when the heart unexpectedly stops beating, leading to loss of consciousness and death)
- Urticaria (hives)
- Hyperhidrosis (excessive sweating)
- Penile haemorrhage (penile bleeding)
- Haematospermia (blood in semen and/or urine)
- Tinnitus (ringing in the ears)
- Haematuria (blood in urine)

Not known (cannot be estimated)
- Stroke
- Myocardial infarction (heart attack)
- Unstable angina pectoris (chest pain)
- Ventricular arrhythmia (abnormal heart rhythm that originates in the lower chambers of the heart)
- Stevens-Johnson syndrome (severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals)
- Exfoliative dermatitis (flaking or peeling skin)
- Retinal vascular occlusion (blood clot in the blood vessels in the eye, which may cause blurred vision or blindness)
- Visual field defect
- Sudden hearing loss

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Yuvanci

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

Do not use Yuvanci 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.

Store in original package in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

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 to protect the environment.

6. Contents of the pack and other information

What Yuvanci contains

The active substances are macitentan and tadalafil.

Each 10 mg/20 mg film-coated tablet contains 10 mg macitentan and 20 mg tadalafil.
Each 10 mg/40 mg film-coated tablet contains 10 mg macitentan and 40 mg tadalafil.

The other ingredients are:

Tablet core

Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose (E463a)
Lactose monohydrate (see section 2 Yuvanci contains lactose)
Magnesium stearate (E470b)
Microcrystalline cellulose (E460i)
Polysorbate 80 (E433)
Povidone (E1201)
Sodium starch glycolate (see section 2 Yuvanci contains sodium)
Sodium lauryl sulfate

Film-coat
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Triacetin (E1518)
Talc (E553b)

Yuvanci 10 mg/20 mg film-coated tablets also contain iron oxide red (E172) and iron oxide yellow (E172).

What Yuvanci looks like and contents of the pack
Yuvanci 10 mg/20 mg film-coated tablets are pink, oblong, tablets debossed with “MT” on one side and “1020” on the other side. Yuvanci 10 mg/20 mg is supplied as 30 × 1 film-coated tablets in aluminium perforated unit dose blisters with integrated desiccant.

Yuvanci 10 mg/40 mg film-coated tablets are white to almost white, oblong, tablets debossed with “MT” on one side and “1040” on the other side. Yuvanci 10 mg /40 mg is supplied as 30 × 1 film-coated tablets in aluminium perforated unit dose blisters with integrated desiccant.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu