1. NAME OF THE MEDICINAL PRODUCT

JESELHY tablets 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each JESELHY tablet contains 40 mg of pimitespib.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

JESELHY tablets 40 mg: White to off-white, round, film-coated tablets debossed with "40" on one side, and "P116" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JESELHY is indicated for the treatment of gastrointestinal stromal tumor (GIST) that has progressed after cancer chemotherapy (including but not limited to Imatinib, Sunitinib, Regorafenib).

4.2 Posology and method of administration

Posology

The recommended dosage of JESELHY is 160 mg of pimitespib administered orally once daily on an empty stomach for 5 consecutive days, followed by 2 days off, and repeated. When administered in the fed state, the C_{max} and AUC of JESELHY increase. To avoid food effects, JESELHY should not be taken between 1 hour before and 2 hours after a meal.

Dose adjustments for toxicity

If an adverse reaction occurs, treatment with JESELHY should be interrupted or the dose reduced according to symptoms and severity, taking into account the following criteria.

Table 1 - Dosage when the dose is reduced

Dose reduction level	Dosage
No reduction	160 mg/day
1-level reduction	120 mg/day
2-level reduction	80 mg/day
3-level reduction	40 mg/day

Table 2 - Criteria for dose interruption or reduction at the onset of adverse reactions

Adverse reaction	Grade*	Action
Diarrhoea	Grade 2	Withhold if the adverse drug reaction (ADR) is difficult to manage and intolerable. Resume dosing at the

		same dose after recovery to ≤ Grade 1.
	≥ Grade 3	Withhold. Resume dosing at a dose reduced by 1 dose level or at the same dose after recovery to ≤ Grade 1.
Eye disorders	≥ Grade 2	Withhold. Resume dosing at a dose reduced by 1 dose level or at the same dose after recovery to ≤ Grade 1.
Other adverse reactions (excluding diarrhoea and eye disorders)	≥ Grade 3	Withhold. Resume dosing at a dose reduced by 1 dose level after recovery to ≤ Grade 2 or at the same dose after recovery to ≤ Grade 1.

*Based on NCI-CTCAE Ver. 4.03 criteria

Posology adjustments for special populations
None

Method of administration

JESELHY is for oral administration.

4.3 Contraindications

JESELHY is contraindicated in patients with a history of hypersensitivity to any of the ingredients of JESELHY.

4.4 Special warnings and precautions for use

Severe diarrhoea
In the JESELHY clinical program, there have been reports of serious renal disorders resulting from dehydration due to diarrhoea.

It is not possible to predict which patients will develop this event. Special attention should be paid to the symptom and consequences of diarrhoea, particularly dehydration and acute kidney injury. Antidiarrheal agents should be used as necessary. Electrolytes should be monitored carefully and fluid replacement considered in order to prevent dehydration and electrolyte shift. Dose modifications (interruption and/or reduction) should be applied as necessary.

Eye disorder
Eye disorder may occur.

Eye disorder should be closely monitored during administration. Efforts should be made to ensure early detection of ocular reactions, including an early ophthalmologic consultation in the event of any persistent or vision-reducing ocular symptoms. Dose interruption / dose reduction should be considered as necessary.

Haemorrhage
Serious ADRs of duodenal ulcer haemorrhage and intra-abdominal haemorrhage were reported.

It is not possible to predict which patients will develop this event. Special attention should be paid to the symptom of haemorrhage. Dose modifications (interruption and/or reduction) should be applied as necessary.

Embryo-fetal toxicity
In an embryo-fetal development toxicity study in rats, growth inhibition, teratogenicity, and embryo-fetal lethality were observed in pregnant rats treated with 4 mg/kg of pimitespib. Although the plasma concentration of pimitespib in pregnant rats is unknown, the plasma concentration of unbound pimitespib at 4 mg/kg in non-pregnant female rats was 0.9-1.5 times and 0.6-1.0 times of that at the clinical therapeutic dose in terms of C_{max} and AUC, respectively. Therefore, it is possible that even the clinical therapeutic dose may affect embryos and fetuses. Genotoxicity studies showed that pimitespib induced chromosomal structural abnormalities, but did not induce mutagenicity or chromosomal numerical aberration.

There are no clinical data on embryo fetal toxicity from the clinical trials.

Since GIST progressed after chemotherapy has a poor prognosis and other treatment options are extremely limited, it is considered that it is acceptable to administer JESELHY with caution to pregnant women or women who may be pregnant, provided that the potential risks to the fetus are fully explained to the patient and her family, and only when the therapeutic benefits are judged to outweigh the risks.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been conducted at the moment. The following information is based on results from *in vitro* studies and physiologically based pharmacokinetic (PBPK) simulations. Caution is advised if these drugs are given concomitantly:

Effect of other medications on pimitespib

- P-gp and BCRP inhibitors or inducers: Pimitespib is a substrate of P-gp and BCRP (*in vitro*). P-gp and BCRP inhibitors or inducers may alter the concentration and activity of pimitespib.

Effect of pimitespib on other medications

- CYP3A substrates: Pimitespib has a potential to time-dependently inhibit CYP3A (*in vitro*) and PBPK simulations suggested that midazolam concentration may be increased when used in combination of pimitespib.
- MATE1 and MATE2-K substrates: Pimitespib has a potential to inhibit MATE1 and MATE2-K (*in vitro*) and PBPK simulations suggested that metformin concentration may be increased when used in combination of pimitespib.
- P-gp, BCRP, and OATP1B1 substrates: Pimitespib has a potential to inhibit P-gp, BCRP, and OATP1B1 (*in vitro*). P-gp, BCRP, and OATP1B1 substrates concentration may be increased when used in combination of pimitespib.

4.6 Fertility, pregnancy and lactation

Fertility
If JESELHY must be administered to a patient with reproductive potential, the possibility that JESELHY can decrease reproductive function should be considered. Animal studies (in rats) have reported increased apoptotic bodies in the vaginal epithelium, multifocal cysts in the ovaries, white patches in the ovaries, decreased corpora lutea, and proliferation of interstitial glands. In addition, animal studies (in rats and dogs) have reported degeneration of the seminiferous tubules, atrophic changes of the accessory sex glands, and degeneration/necrosis of the germinal epithelium, accompanied by decreased spermatozoa in the epididymis.

Pregnancy
Women of childbearing potential should be instructed to use appropriate contraception during treatment with JESELHY and for an appropriate period after the end of treatment.

In genotoxicity studies, JESELHY induced structural chromosomal aberrations. Men whose partner is of childbearing potential should be instructed to use appropriate contraception during treatment with pimitespib and for an appropriate period after the end of treatment.

Pregnant women or women who may be pregnant should be administered only when the therapeutic benefit is judged to outweigh the risk. An embryo-fetal development study in rats reported growth inhibition, teratogenicity, and embryonic death in embryos and fetuses at exposure doses below the clinical exposure dose (AUC).

Breast-feeding
It is advisable not to breastfeed while taking JESELHY. It may be excreted in human milk, and serious adverse reactions may occur in an infant with exposure to JESELHY through milk.

4.7 Effects on ability to drive and use machines

There was no report of the effects of JESELHY on the ability to drive or use machines from the studies that have been conducted so far.

4.8 Undesirable effects

Tabulated list of adverse drug reactions

Table 3 shows the adverse drug reactions of JESELHY reported in the Blinded Administration Period and/or the Unblinded Administration period of Study 10058030.

Table 3 - Adverse drug reactions of JESELHY (Study 10058030: Blinded Administration Period and/or the Unblinded Administration Period)

MedDRA [a] (Version 23.0)	**ADRs (Preferred Term) (N=75)**		
System Organ Class	≥ 10%	5% to < 10%	< 5%
Blood and lymphatic system disorders		Anaemia	
Endocrine disorders			Hypothyroidism
Eye disorders	Night blindness	Vision blurred, visual impairment	Retinal vein occlusion, retinopathy, colour blindness acquired
Gastrointestinal disorders	Diarrhoea, nausea	Vomiting	Abdominal discomfort, abdominal pain, dry mouth, dyspepsia, enterocolitis, stomatitis, intra-abdominal haemorrhage, duodenal ulcer haemorrhage
General disorders and administration site conditions	Malaise		Oedema, pyrexia
Hepatobiliary disorders		Liver disorder	
Infections and infestations			Pneumonia, cystitis

MedDRA [a] (Version 23.0)	**ADRs (Preferred Term) (N=75)**		
System Organ Class	≥ 10%	5% to < 10%	< 5%
Investigations	Blood creatinine increased	Alanine aminotransferase increased, aspartate aminotransferase increased	Platelet count decreased, blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, weight decreased, blood phosphorus decreased
Metabolism and nutrition disorders	Decreased appetite		Hypokalaemia, dehydration,
Nervous system disorders	Taste disorder		
Renal and urinary disorders	Renal impairment		Proteinuria, dysuria
Respiratory, thoracic and mediastinal disorders			Dysphonia
Skin and subcutaneous tissue disorders		Rash	Alopecia, pruritus, dermatitis acneiform, eczema, rash maculo-papular

[a] Medical Dictionary for Regulatory Activities

Post-Marketing Experience
There is post-marketing experience only in Japan, and it is limited.

4.9 Overdose

There is limited clinical experience of an overdose with JESELHY.
There is no known antidote for JESELHY. In the event of overdose, the patient should be monitored for adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, heat shock protein 90 inhibitor

Mechanism of action
Pimitespib inhibits heat shock protein 90 (HSP90), a molecular chaperone that contributes to the stabilization of proteins, thereby leading to decrease the amounts of various client proteins, which are essential for the proliferation and survival of cancer cells.

Pimitespib inhibited the growth of the GIST-T1 human gastrointestinal stromal tumor-derived cell line (*in vitro*).

Pimitespib inhibited the tumor growth in the GIST-T1 human gastrointestinal stromal tumor xenograft mouse model (*in vivo*).

Pharmacodynamic effects

Two pharmacodynamics studies investigated the effects of pimitespib administration on biomarkers. In the first study, nude mice were administered pimitespib orally (5 mg/kg or 10 mg/kg) once, and heat shock protein 70 (HSP70) expression in peripheral blood mononuclear cells (PBMC) was measured. Dose-dependent induction of HSP70 was observed with this single administration of pimitespib. In the second study, nude mice bearing NCI-N87 tumor xenograft were administered pimitespib orally (5 mg/kg or 10 mg/kg once daily [QD]) for 14 days. Significant antitumor effect was observed in mice administered 5 mg/kg pimitespib, and a greater effect was observed in the 10 mg/kg group. Dose and time dependency of induction of HSP70 protein in PBMC as indicators for target engagement were also assessed. Both studies indicated that HSP70 protein expression in PBMC is a useful parameter for target engagement.

In clinical study 10058010, the induction of HSP70 after repeated administration of JESELHY occurred in a dose-dependent manner.

Clinical efficacy and safety

Phase 3 study (10058030 study)

JESELHY at 160 mg or placebo was orally administered to 86 patients with unresectable or metastatic gastrointestinal stromal tumor that has progressed [Note 1)] after imatinib, sunitinib, and regorafenib once daily for 5 consecutive days, followed by 2 days off repeatedly. The treatment with JESELHY significantly prolonged progression-free survival based on modified RECIST ver. 1.1 [Note 2)] compared with placebo, of primary endpoint. (data cut-off; 23 June 2020)

Note 1) Patients with progression based on RECIST or clinical progression or intolerance to treatment with imatinib, sunitinib, and regorafenib were included.

Note 2) The following modified criteria were used from the standard RECIST ver. 1.1.

1. Selection of any lymph nodes as target lesions is not permitted.
2. Criteria for evaluation of new tumor nodule within pre-existing tumor mass

(i) Tumor nodules within a pre-existing tumor mass that have a longest dimension of ≥ 2 cm and definitively active lesions enhanced with dynamic CT.

(ii) Lesions will be met on at least two sequential tumor assessments, which must be left at least ≥ 21 days between tumor assessments.

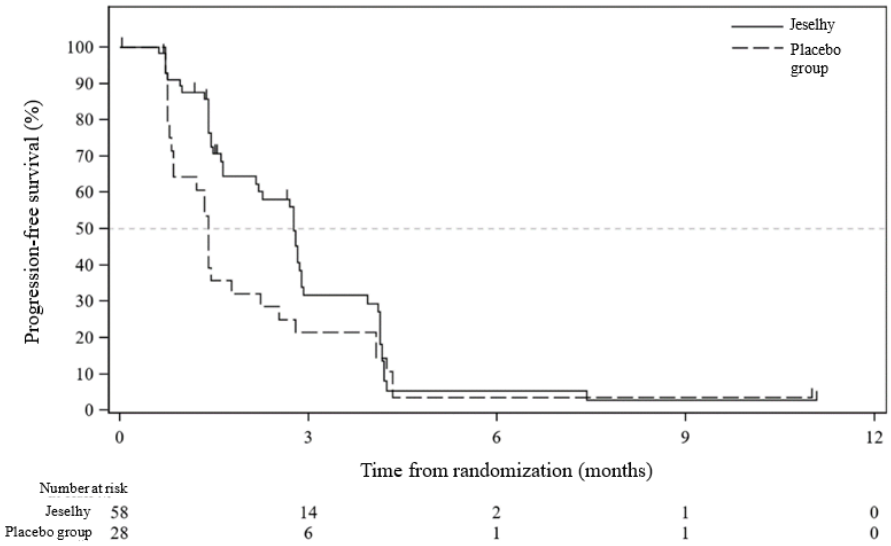
Table 4 - Progression-free survival results

Treatment group	**No. of patients**	**Median progression-free survival (months) (95% confidence interval)**	**p-value (one-sided)[Note 3)]**	**Hazard ratio[Note 4)] (95% confidence interval)**
JESELHY	58	2.8 (1.6, 2.9)	0.006	0.51 (0.30, 0.87)
Placebo	28	1.4 (0.9, 1.8)		

Note 3) Stratified log-rank test.

Note 4) Comparison with placebo per a Cox proportional hazard model.

Figure 1 - Kaplan–Meier curves of the progression-free survival



Adverse reactions occurred in 70 (93.3%) of 75 patients receiving JESELHY [Note 5)]. Major adverse reactions included diarrhoea (54 patients, 72%), decreased appetite (22 patients, 29.3%), blood creatinine increased (21 patients, 28%), malaise (20 patients, 26.7%), nausea (19 patients, 25.3%), renal impairment (10 patients, 13.3%), and night blindness (9 patients, 12%).

Note 5) 58 patients receiving JESELHY and 17 patients crossed-over to JESELHY

5.2 Pharmacokinetic properties

The pharmacokinetic parameters of pimitespib following the repeated oral administration of 160 mg JESELHY once daily on an empty stomach in Japanese patients with advanced solid tumors (n = 22) are shown in the table below. Following the repeated administration of 160 mg JESELHY once daily on an empty stomach, the accumulation rate of pimitespib at Day 5 was 1.27 times.

Table 5 - Pharmacokinetic parameters following repeated oral administration of JESELHY at 160 mg once daily

PK parameter (unit)	Day 1 (n = 22)	Day 5 (n = 22)
T_{max} (hr)	3.87 (1.00 to 8.00)	2.98 (1.00 to 7.98)
C_{max} (ng/mL)	2263 ± 758	2600 ± 942
AUC_{last} (ng·hr/mL)	28394 ± 7351	35277 ± 12003
AUC_{inf} (ng·hr/mL)	38570 ± 9686 [a]	NC
$T_{1/2}$ (hr)	11.22 ± 3.48 [a]	10.40 ± 2.32 [a]

Mean ± standard deviation; median (minimum to maximum) only for T_{max}; NC, not calculated; [a] n = 18

Absorption

Effect of Food

Following a single oral administration of 160 mg JESELHY in Japanese patients with advanced solid tumors (n = 16), the geometric mean ratios of C_{max} and AUC_{inf} of pimitespib in the fed state compared those in the fasted state were 1.92 and 1.64, respectively.

Distribution

The plasma protein binding ratio of pimitespib ranged 93.1%–93.6%. Pimitespib primarily bound to albumin fraction in the human plasma *(in vitro)*. The blood-to-plasma concentration ratio of pimitespib ranged 0.525–0.630 in humans *(in vitro)*.

Biotransformation
Pimitespib is primarily metabolized by CES1 *(in vitro)*. Following the repeated oral administration of 150.5 mg/m^2 JESELHY to three patients with advanced solid tumors, unchanged pimitespib, an amide hydrolyzed product, and *N*-demethylated product were observed in the urine by 24 hours after administration.

Elimination
Following the oral administration of 107.5 mg/m^2 JESELHY to Japanese patients with advanced solid tumors (n = 6), the urinary excretion rate of unchanged pimitespib was 2.2% of dose by 24 hours after administration.

Pharmacokinetics in special populations
No dedicated pharmacokinetics studies for elderly, liver and renal impairment was conducted at the moment.

Based on the results of population pharmacokinetics analysis, age, liver and renal function were found not to be predictors of pimitespib pharmacokinetics.

5.3 Preclinical safety data

General toxicity
Major toxicity target organs of pimitespib in the rats and dogs included the lymphohematopoietic tissue, hepatobiliary tissue, gastrointestinal tract, kidneys, adrenal glands, reproductive organs, skin, and bones. In dead and moribund animals, changes were also observed in the salivary glands, mammary glands, and trachea. The toxicities of pimitespib were observed in these organs at systemic exposures in the range of or below the anticipated human exposure level based on the unbound AUC comparison. In 4-week repeated oral dosing of pimitespib followed by a 4-week drug cessation, all these toxicity showed complete recovery or a tendency towards recovery in rats and dogs.

Impairment of Fertility:
In a reproductive and developmental toxicity study, pimitespib exhibited growth inhibition effect, teratogenicity, and embryo-fetal lethality in rat embryo-fetus at the maternal toxic dosage. The no observed adverse effect level (NOAEL) was 2 mg/kg for dams and embryo-fetal development.

No specific studies on fertility have been performed. However, pimitespib induced increased apoptotic bodies in the vaginal epithelium, multifocal cysts in the ovaries, white patch in the ovary, decreased corpus luteum, and proliferation of interstitial gland in the repeated oral dose toxicity studies in rats. In addition, degeneration of the seminiferous tubule, atrophic changes of the accessory sex glands, and degeneration/necrosis of the germinal epithelium, accompanied by a decreased spermatozoa in the epididymis, were observed in rats or dogs. Therefore, a potential of pimitespib to adversely affect reproduction has to be considered.

Carcinogenicity:
No carcinogenicity studies have been conducted.

Genotoxicity:
In a reverse mutation test (Ames test), pimitespib had no effect. In contrast, in the chromosomal aberration test, the percentage of Chinese hamster lung cells (CHL/IU) with structural chromosome aberrations increased after 24 hours of treatment with pimitespib, indicating that pimitespib has clastogenic potential. In the bone marrow micronucleus test in rats, the percentage of reticulocytes with micronucleus increased at 30 mg/kg, indicating that pimitespib can induce micronuclei. Based on these results, pimitespib is considered to be genotoxic (structural chromosomal aberrations).

Environmental risk assessment (ERA)
No environmental risk assessment studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose hydrate
Corn starch
Hydroxypropylcellulose
Microcrystalline cellulose
Magnesium stearate

Film coating
Hypromellose
Macrogol 6000
Titanium oxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30ºC.

6.5 Nature and contents of container

Blister packs are supplied in carton boxes.
Each blister pack contains 10 tablets.
Pack size of 40 film-coated 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

Diethelm Keller Logistics Limited, Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 29/67 (NC)

9. DATE OF FIRST AUTHORISATION

25 September 2024

10. DATE OF REVISION OF THE TEXT

Sep 2024