# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

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

## 1. NAME OF THE MEDICINAL PRODUCT

Rytelo 47 mg powder for concentrate for solution for infusion
Rytelo 188 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rytelo 47 mg powder for concentrate for solution for infusion

Each vial contains imetelstat sodium equivalent to 47 mg imetelstat.
After reconstitution, 1 mL of the solution contains 31.4 mg imetelstat.

Rytelo 188 mg powder for concentrate for solution for infusion

Each vial contains imetelstat sodium equivalent to 188 mg imetelstat.
After reconstitution, 1 mL of the solution contains 31.4 mg imetelstat.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white or slightly yellow lyophilised powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Rytelo is indicated as monotherapy for the treatment of adult patients with transfusion-dependent anaemia due to very low, low or intermediate risk myelodysplastic syndromes (MDS) without an isolated deletion 5q cytogenetic (non-del 5q) abnormality and who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy (see section 5.1).

### 4.2 Posology and method of administration

Rytelo should be administered and monitored under the supervision of physicians and healthcare professionals who are experienced in haematologic disease and treatment.

Complete blood cell count and liver function tests are recommended before administration of each dose. Additionally, weekly blood cell counts are recommended following the first two doses (see section 4.4).

A pregnancy test should be performed before administration of the first dose of Rytelo for females of reproductive potential (see section 4.6).

Posology

The recommended dose of Rytelo is 7.1 mg/kg body weight administered as an intravenous infusion once every 4 weeks. Rytelo should be discontinued if patients do not experience a reduction in red blood cell (RBC) transfusion burden after 24 weeks of treatment (6 doses) or if unacceptable toxicity occurs at any time.

*Premedication for potential infusion-related reactions*

Patients should be premedicated with diphenhydramine (25 to 50 mg) and hydrocortisone (100 to 200 mg), or equivalent, at least 30 minutes before dosing with Rytelo. Premedication should be administered before any doses of Rytelo, to prevent or reduce potential infusion-related reactions (see section 4.4).

*Dose modifications*

Recommended dose reductions for all Grade 3 and Grade 4 adverse reactions are found in Table 1.

The management of Grade 3 and Grade 4 adverse reactions may require a dose delay, dose reduction, or treatment discontinuation and are presented in Table 2, Table 3 and Table 4. Treatment with Rytelo should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg.

**Table 1: Recommended dose reduction for all Grade 3 and Grade 4 adverse reactions**

| **Dose reduction** | **Current dose** | **Decreased dose** |
|---|---|---|
| First dose reduction | 7.1 mg/kg | 5.6 mg/kg |
| Second dose reduction | 5.6 mg/kg | 4.4 mg/kg |

*Grade 3 and Grade 4 haematologic adverse reactions*

Delay administration of Rytelo if absolute neutrophil count is less than $1.0 \times 10^9$/L or platelets are less than $50 \times 10^9$/L. Modify dose as described in Table 2.

**Table 2: Dose modifications for Grade 3 and Grade 4 haematologic adverse reactions**

| Adverse reaction | Severity grade[a, b] | Occurrence | Treatment modification |
|---|---|---|---|
| **Thrombocytopenia** (see sections 4.4 and 4.8) | Grade 3 | First | • Delay treatment until platelets are ≥ 50 × $10^9$/L<br>• Restart at same dose level |
| | | Second and third | • Delay treatment until platelets are ≥ 50 × $10^9$/L<br>• Restart at one dose level lower |
| | Grade 4 | First and second | • Delay treatment until platelets are ≥ 50 × $10^9$/L<br>• Restart at one dose level lower |
| **Neutropenia** (see sections 4.4 and 4.8) | Grade 3 | First | • Delay treatment until absolute neutrophil counts are ≥ 1.0 × $10^9$/L<br>• Restart at same dose level |
| | | Second and third | • Delay treatment until absolute neutrophil counts are ≥ 1.0 × $10^9$/L<br>• Restart at one dose level lower |
| | Grade 4 | First and second | • Delay treatment until absolute neutrophil counts are ≥ 1.0 × $10^9$/L<br>• Restart at one dose level lower |

[a] Severity based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.
[b] Grade 3: severe; Grade 4: life-threatening

*Non-haematologic adverse reactions*

Dose administration modifications for infusion-related reactions are described in Table 3.

**Table 3: Dose administration modifications for infusion-related reactions**

| Adverse reaction | Severity grade[a, b] | Occurrence | Treatment modification |
|---|---|---|---|
| **Infusion-related reactions** (see sections 4.4 and 4.8) | Grade 2 or 3 | First and second | • Interrupt the infusion until resolution or the intensity of the adverse reactions decrease to Grade 1[b]<br>• Restart infusion at 50% of the infusion rate administered prior to the adverse reactions (i.e., 125 mL/h) |
| | | Third | • For Grade 2, stop infusion. May restart at next dose administration<br>• For Grade 3, discontinue treatment |
| | Grade 4 | First | • Stop infusion<br>• Administer supportive care as appropriate and discontinue treatment |

[a] Severity based on NCI CTCAE, version 4.03.
[b] Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening

Dose modifications for other adverse drug reactions, including elevated liver function tests, are described in Table 4.

**Table 4: Dose modifications for non-haematologic adverse reactions**

| Adverse reaction | Severity grade[a, b] | Occurrence | Treatment modification |
|---|---|---|---|
| **Other adverse drug reactions including elevated liver function tests** (see section 4.8) | Grade 3 or 4 | First and second | • Delay treatment until adverse reactions are Grade 1[b] or at baseline Grade<br>• Restart at one dose level lower |

[a] Severity based on NCI CTCAE, version 4.03.
[b] Grade 1: mild; Grade 3: severe; Grade 4: life-threatening

*Missed doses*

If a planned dose is missed, the patient should be administered Rytelo as soon as possible and dosing continued as prescribed with 4 weeks between doses.

Special populations

*Elderly*

No dose adjustments are required in elderly patients (≥ 65 years of age).

*Renal impairment*

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCL] 30 to < 90 mL/min). There is insufficient data in patients with severe renal impairment (CrCL 15 to < 30 mL/min) or end-stage renal disease to support a dose recommendation (see section 5.2).

*Hepatic impairment*

No dose adjustment is required in patients with mildly to moderately abnormal liver function tests (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin > 1× to 1.5× ULN (Grade 1) and any AST) or (total bilirubin > 1.5× to 3× ULN (Grade 2) and any AST). There is insufficient data in patients with severely abnormal liver function tests (total bilirubin > 3× ULN (Grade 3) and any AST) to support a dose recommendation (see section 5.2).

*Paediatric population*

The safety and efficacy of Rytelo in children and adolescents aged 28 days to less than 18 years have not yet been established. No data are available.

There is no relevant use of Rytelo in paediatric patients aged less than 28 days.

Method of administration

Rytelo is for intravenous use.

Rytelo is provided for single use only.

Rytelo must be reconstituted and diluted using aseptic technique under the supervision of a healthcare professional before administration as an intravenous infusion.

Administer the intravenous infusion over 2 hours (i.e., 250 mL/h). For reduced infusion rates that may be necessary due to infusion related reactions, see Table 3 in section 4.2. Do not administer as an intravenous push or bolus.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Thrombocytopenia

Thrombocytopenia has been reported during treatment with Rytelo, including new or worsening Grade 3 or Grade 4 thrombocytopenia (see section 4.8). Complete blood cell counts should be monitored prior to each dose of Rytelo, weekly following administration of the first two doses, and for any case of Grade 3 or Grade 4 thrombocytopenia or as clinically indicated. Patients with Grade 3 or Grade 4 thrombocytopenia should be monitored for bleeding events as a precaution. The need for platelet transfusions should be assessed as clinically appropriate. Patients should be advised to report any signs or symptoms of bruising or bleeding immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended (see section 4.2).

Neutropenia

Neutropenia has been reported during treatment with Rytelo, including new or worsening Grade 3 or Grade 4 neutropenia (see section 4.8), and febrile neutropenia may occur. Complete blood cell counts should be monitored prior to each dose of Rytelo, weekly following administration of the first two doses, and for any case of Grade 3 or Grade 4 neutropenia. Patients with Grade 3 or Grade 4 neutropenia should be monitored for infections, including sepsis as a precaution. Granulocyte-colony stimulating factors and anti-infective therapies should be administered as clinically indicated. Patients should be advised to report any signs or symptoms of neutropenia, such as fever or infection immediately. The next dose should be delayed and resumed at the same or reduced dose as recommended (see section 4.2).

Infusion-related reactions

Infusion-related reactions have been reported during treatment with Rytelo and were generally mild or moderate in severity (see section 4.8). The most common symptoms were headache and back pain. Other notable adverse reactions were Grade 3 hypotension, hypertension, hypertensive crisis, and non-cardiac chest pain. Patients usually experienced an infusion-related reaction during or shortly after the end of the infusion.

Patients should receive premedication at least 30 minutes prior to dosing with Rytelo to reduce the risk of experiencing infusion-related reactions (see section 4.2). Patients should be monitored for adverse reactions for at least one hour after the infusion has been completed.

Manage symptoms of infusion-related reactions with supportive care and consider interrupting the infusion, decreasing the infusion rate, or discontinuing treatment based on the severity and frequency of occurrence as recommended (see section 4.2).

Embryo-foetal toxicity

Based on findings in animals, Rytelo may cause embryo-foetal harm when administered to a pregnant woman. Administration of imetelstat to pregnant mice and rabbits during the period of organogenesis resulted in embryo-foetal mortality at maternal exposures (AUC) ≥ 3.4 times the human exposure at the recommended clinical dose (see section 5.3).

Pregnant women should be advised of the potential risk to a foetus. Women of child-bearing potential should be advised to use effective contraception during treatment with Rytelo and for at least 1 week after the last dose (see section 4.6).

Excipients with known effect

*Sodium*

This medicinal product contains 35 mg sodium (the dose of a patient weighing 80 kg) per dose or approximately 1.8% of the World Health Organization (WHO) recommended maximum daily intake of 2 g sodium for an adult.

Additional sodium will be introduced through a sodium-containing solution used for preparation for administration (see section 6.6). This should be considered in relation to the total sodium intake to the patient from all sources per day.

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

No interaction studies have been performed in humans (see section 5.2).

*In vitro* imetelstat is an inhibitor of BCRP, OAT1, OATP1B1 and OATP1B3 at concentrations similar to those reached on the day of imetelstat administration. The risk for an interaction, causing increased plasma concentrations of a co-administrated substrate, declines with the rapidly declining plasma concentrations of imetelstat and is likely not relevant on the following days of the dose interval.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in women

The pregnancy status of females of reproductive potential should be verified before starting treatment with Rytelo (see section 4.2).

Women of childbearing potential should be advised to use effective contraception during treatment with Rytelo and for at least 1 week after the last dose.

Pregnancy

There are no data on the use of imetelstat in pregnant women. Studies in animals have shown that imetelstat may cause embryonic or foetal loss (see section 5.3). Imetelstat is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether imetelstat is excreted in human milk.

There is no data on the presence of imetelstat in human milk, the effects on the breastfed child, or the effects on milk production. A risk to the breast-feeding child cannot be excluded. Because of the potential for adverse reactions in breast-fed children, women should be advised not to breastfeed during treatment with Rytelo and for 1 week after the last dose.

Fertility

Based on findings in animals, imetelstat may impair fertility in females of reproductive potential (see section 5.3). No human data on the effect of imetelstat on fertility are available.

## 4.7 Effects on ability to drive and use machines

Rytelo may have a minor influence on the ability to drive and use machines. The ability to react when performing these tasks may be impaired due to the potential effects of asthenia and infusion-related reactions, such as malaise, chest pain, and hypertensive crisis following treatment administration (see section 4.8).

Patients should be advised to use caution until any symptoms affecting their ability to drive or operate machines have resolved.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with Rytelo were thrombocytopenia (94%), leukopenia (93%), neutropenia (92%), aspartate aminotransferase (AST) increased (48%), alanine aminotransferase (ALT) increased (42%), alkaline phosphatase (ALP) increased (41%), asthenia (26%) and headache (16%).

The most commonly reported severe adverse reactions (Grade ≥ 3) were neutropenia (69%) and thrombocytopenia (63%).

The most commonly reported serious adverse reactions were sepsis (1.7%), urinary tract infection (1.7%), atrial fibrillation (1.1%), oesophageal varices haemorrhage (1.1%), syncope (1.1%), and thrombocytopenia (1.1%).

The frequency of treatment discontinuation due to adverse reactions was 13%. The most common adverse reactions leading to treatment discontinuation were thrombocytopenia (6.3%) and neutropenia (6.3%).

The frequency of dose reduction or dose delay due to adverse reactions is 65%. The most common adverse reactions leading to dose modification or interruption were neutropenia (51%) and thrombocytopenia (45%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from the clinical trials in 175 patients with low to intermediate-1 risk MDS, transfusion-dependent anaemia and were either relapsed or refractory to or ineligible for ESA treatment and treated with imetelstat at the recommended dose. Patients were treated with Rytelo for a median of 7.8 months.

The adverse reactions are listed below by MedDRA system organ class and by frequency within each system organ class, with the most frequent adverse reactions listed first. Frequencies were defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

**Table 5: Adverse reactions in low to intermediate-1 risk MDS patients treated with Rytelo in Phase 2 and 3 MDS3001 study**

| System organ class | Adverse reaction | Frequency (all grades) | All grades (N = 175) | Grades ≥ 3 (N = 175) |
|---|---|---|---|---|
| **Infections and infestations** | Urinary tract infection[a] | Very common | 12% | 2.3% |
| | Sepsis[b] | Common | 4.0% | 4.0% |
| **Blood and lymphatic system disorders** | Thrombocytopenia[c] | Very common | 94% | 63% |
| | Neutropenia[c] | Very common | 92% | 69% |
| | Leukopenia[c] | Very common | 93% | 56% |
| **Immune system disorders** | Infusion-related reactions[d] | Common | 8.6% | 3.4% |
| **Nervous system disorders** | Headache | Very common | 16% | 1.7% |
| | Syncope[e] | Common | 4.6% | 1.7% |
| **Cardiac disorders** | Atrial fibrillation[f] | Common | 3.4% | 1.1% |
| **Vascular disorders** | Haematoma | Common | 5.7% | 0.6% |
| **Respiratory, thoracic and mediastinal disorders** | Epistaxis | Common | 5.1% | 0 |
| **Gastrointestinal disorders** | Gastrointestinal bleeding[g] | Common | 6.3% | 1.7% |
| **Hepatobiliary disorders** | Aspartate aminotransferase increased[c] | Very common | 48% | 2.3% |
| | Alanine aminotransferase increased[c] | Very common | 42% | 4.0% |
| | Alkaline phosphatase increased[c] | Very common | 41% | 0 |
| **Skin and subcutaneous tissue disorders** | Pruritus | Common | 5.1% | 0 |
| **Musculoskeletal and connective tissue disorders** | Arthralgia | Common | 6.9% | 0 |
| **Renal and urinary disorders** | Haematuria | Common | 4.6% | 1.1% |
| **General disorders and administration site conditions** | Asthenia[h] | Very common | 26% | 0.6% |

[a] Urinary tract infection includes urinary tract infection, Escherichia urinary tract infection, and cystitis.
[b] Sepsis includes sepsis, enterococcal sepsis, escherichia sepsis, neutropenic sepsis, and urosepsis.
[c] Thrombocytopenia (platelet count decreased), neutropenia (neutrophil count decreased), leukopenia (white blood cell count decreased), AST increased, ALP increased, and ALT increased are based on laboratory values.
[d] Infusion-related reactions include abdominal pain, abdominal pain upper, arthralgia, asthenia, back pain, bone pain, chest pain, diarrhoea, discomfort, dyspnoea, erythema, flushing, headache, hyperhidrosis, hypertension, hypertensive crisis, hypotension, illness, malaise, nausea, non-cardiac chest pain, oedema peripheral, palmar erythema, pruritus, pyrexia, spinal pain, urticaria, and vomiting. Only events considered related to infusion-related reactions are included.
[e] Syncope includes loss of consciousness, presyncope, and syncope.
[f] Atrial fibrillation includes atrial fibrillation and atrial flutter.
[g] Gastrointestinal bleeding includes anal haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematochezia, haemorrhoidal haemorrhage, intestinal haemorrhage, rectal haemorrhage, and oesophageal varices haemorrhage.
[h] Asthenia includes asthenia and fatigue.

Description of selected adverse reactions

*Thrombocytopenia*

Thrombocytopenia occurred in 94.3% of patients receiving imetelstat. Incidences of Grade 3 or Grade 4 thrombocytopenia were 62.9%. Median time to first onset of ≥ Grade 3 events was 5 (range: 1.7, 89.7) weeks. Median duration of thrombocytopenia for ≥ Grade 3 events was 1.4 (range: 0.1, 15.0) weeks. (see sections 4.2 and 4.4) Thrombocytopenia (treatment-emergent adverse events of any Grade) led to dose reduction or cycle delay in 24.6% and 44.6% of patients, respectively. Treatment was permanently discontinued in 6.3% of patients.

*Neutropenia*

Neutropenia occurred in 92.0% of patients receiving imetelstat. Incidences of Grade 3 or Grade 4 neutropenia were 69.1%. Median time to first onset of ≥ Grade 3 events was 4.3 (range: 1.0, 118.6) weeks. Median duration of neutropenia for ≥ Grade 3 events was 2.0 (range:0.0, 16.7) weeks. (see sections 4.2 and 4.4) Neutropenia (treatment-emergent adverse events of any Grade) led to dose reduction or cycle delay in 36.6% and 50.3% of patients, respectively. Treatment was permanently discontinued in 6.3% of patients.

*Infusion-related reactions*

Infusion-related reactions occurred in 8.6% of patients receiving imetelstat. Incidences of Grade 3 or Grade 4 infusion-related reactions were 3.4%. Infusion-related reactions were generally mild or moderate in severity. The most common infusion-related reactions were headache (3.4%) and back pain (2.3%). Other notable infusion-related reactions were Grade 3 events of hypotension (0.6%), hypertension (0.6%), hypertensive crisis (0.6%), and non-cardiac chest pain (0.6%). Infusion-related reactions usually occurred during or shortly after the end of the infusion (see sections 4.2 and 4.4). Infusion-related reactions led to dose reduction or cycle delay in 0.6% of patients or in temporary interruption or termination of the infusion in 5.7% of patients. Treatment was permanently discontinued in 0.6% of patients.

*Hepatobiliary disorders*

AST increased, ALT increased, and ALP increased occurred in 48.0%, 41.7%, and 41.1% of patients receiving imetelstat, respectively. Incidences of Grade 3 or Grade 4 events were 2.3%, 4.0%, and 0%, respectively. Median time to first onset of Grade ≥ 3 events was 30.4 (range: 25.9, 63.1) weeks for AST increased and 32.0 (range: 1.0, 84.1) weeks for ALT increased. Median duration of Grade ≥ 3 events was 1.2 (range:0.4, 2.4) weeks for AST increased and 1.5 (range:0.7, 4.0) weeks for ALT increased. Events (treatment-emergent adverse events of any Grade) led to cycle delay in 1.7% of patients for AST increased and 0.6% for ALT increased. No event led to discontinuation of treatment.

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

In case of overdose or incorrect administration (such as intravenous push or bolus), patients should be monitored for any signs or symptoms of adverse reactions, and appropriate symptomatic treatment and standard supportive care should be given.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, Other antineoplastic agents, ATC code: L01XX80

Mechanism of action

Imetelstat is an oligonucleotide telomerase inhibitor that binds to the template region of the RNA component of human telomerase (hTR), which prevents telomere binding.

Telomerase activity and human telomerase reverse transcriptase (hTERT) RNA expression are known to be significantly increased in MDS and malignant stem and progenitor cells. Imetelstat treatment leads to reduction of telomere length, inhibition of malignant stem and progenitor cell proliferation and induction of apoptotic cell death leading to reduction of malignant clones.

Pharmacodynamic effects

*Immunogenicity*

During treatment with imetelstat at the recommended dose, anti-drug antibodies (ADA) were detected in 17% of participants. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Clinical efficacy and safety

The efficacy of imetelstat was evaluated in a Phase 3, randomised, double-blind, placebo-controlled, multicentre IMerge trial (MDS3001) in 178 adult patients enrolled with International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS who were transfusion-dependent (requiring ≥ 4 red blood cell (RBC) units over an 8-week period during the 16 weeks prior to randomisation). The diagnosis of MDS for inclusion was based on the WHO 2008 classification. Eligible patients were required to have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs); and had an absolute neutrophil count of $1.5 \times 10^9$/L or greater and platelets $75 \times 10^9$/L or greater. Patients were ineligible if they had a deletion 5q (del5q) cytogenetic abnormality or received prior treatment with lenalidomide or hypomethylating agents.

Participants were randomised in a 2:1 ratio to receive an intravenous infusion of imetelstat (n = 118) 7.1 mg/kg or placebo (n = 60) administered over 2 hours once every 4 weeks until disease progression, unacceptable toxicity, or withdrawal from the study. Randomisation was stratified by prior RBC transfusion burden and by IPSS risk group. Patients were pretreated with an antihistamine and a corticosteroid prior to dosing to mitigate infusion-related reactions. Dose delays or dose reductions for Grade 3 or Grade 4 toxicities observed at the time of the next planned dose were evaluated according to the specified dose modifications (see section 4.2). All patients received supportive care, which included RBC transfusions.

Of the 178 patients enrolled, 62% were male, and 80% White. The median age was 72 years (range: 39 to 87 years) with 20% (36/178) of patients < 65, 47% (84/178) ≥ 65 to < 75, and 33% (58/178) ≥ 75 years of age. A total of 118 patients received imetelstat for a median of 7.8 months (range: 0.03 to 32.5 months) and 59 patients received placebo for a median of 6.5 months (range: 0.03 to 26.7 months). The median follow-up time was 19.5 months (range: 1.4 to 36.2) in the imetelstat group and 17.5 months (range: 0.7 to 34.3) in the placebo group. The key baseline disease characteristics of the efficacy population are shown in Table 6.

**Table 6: Baseline disease characteristics of patients with MDS in Phase 3 study MDS3001**

| Disease characteristics | Imetelstat (N = 118) | Placebo (N = 60) |
|---|---|---|
| **Time since original diagnosis** | | |
| Median years | 3.5 | 2.8 |
| **ECOG score (0, 1, 2), n (%)** | | |
| 0: Asymptomatic | 42 (35.6) | 21 (35) |
| 1: Symptomatic fully ambulatory | 70 (59.3) | 39 (65) |
| 2: Symptomatic in bed less than 50% of the day | 6 (5.1) | 0 |
| **IPSS risk classification, n (%)** | | |
| Low | 80 (67.8) | 39 (65) |
| Intermediate-1 | 38 (32.2) | 21 (35) |
| **Prior RBC transfusion burden[a], n (%)** | | |
| 4 to 6 units | 62 (52.5) | 33 (55) |
| > 6 units | 56 (47.5) | 27 (45) |
| **WHO classification (2008), n (%)** | | |
| RS+[b] | 73 (61.9) | 37 (61.7) |
| RS-[c] | 44 (37.3) | 23 (38.3) |
| Missing | 1 (0.8) | 0 |
| **Baseline serum erythropoietin (EPO), n (%)** | | |
| ≤ 500 mU/mL | 87 (73.7) | 36 (60) |
| > 500 mU/mL | 26 (22) | 22 (36.7) |
| Missing | 5 (4.2) | 2 (3.3) |
| **Prior ESA use, n (%)** | | |
| Yes | 108 (91.5) | 52 (86.7) |
| No | 10 (8.5) | 8 (13.3) |

Abbreviations: ECOG = Eastern cooperative oncology group; ESA = erythropoiesis-stimulating agent; IPSS = International Prognostic Scoring System; MDS = Myelodysplastic syndromes; RS+ = ring sideroblast positive; RS- = ring sideroblast negative; WHO = World Health Organization.

[a] Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to randomisation.

[b] RS+ includes: refractory anaemia with ring sideroblasts (RARS)/refractory cytopenia with multilineage dysplasia and ≥ 15% ringed sideroblasts (RCMD-RS).

[c] RS- includes: others.

Efficacy was determined based on the proportion of patients who achieved 8-week and 24-week red blood cell transfusion independence (RBC-TI). RBC-TI is presented as the absence of RBC transfusion(s) during any consecutive 8-week (56-day) period, and during any consecutive 24-week (168-day) period respectively, regardless of treatment discontinuations or use of subsequent anti-cancer therapy (treatment-policy strategy). The efficacy results are summarised in Table 7.

**Table 7: Efficacy results in Phase 3 study MDS3001**

| | Imetelstat (N = 118) | Placebo (N = 60) |
|---|---|---|
| **Rate of ≥ 8-week RBC TI in the First 24 weeks[a]** | | |
| ≥ 8-week RBC TI, n (%) | 36 (30.5) | 6 (10.0) |
| 95% CI for response rate (%)[b] | (22.4, 39.7) | (3.8, 20.5) |
| % Difference (95% CI)[c] | 20.5 (6.8, 31.5) | |
| *p*-value[d] | 0.002 | |
| **Rate of ≥ 24-week RBC TI in the First 48 weeks[a]** | | |
| ≥ 24-week RBC TI, n (%) | 30 (25.4) | 2 (3.3) |
| 95% CI for response rate (%)[b] | (17.9, 34.3) | (0.4, 11.5) |
| % Difference (95% CI)[c] | 22.1 (10.3, 31.5) | |
| *p*-value[d] | < 0.001 | |

CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

[a] TI regardless of treatment discontinuations or use of subsequent anti-cancer therapy (treatment-policy strategy).
[b] The 95% CI for response rate based on Exact Clopper-Pearson confidence interval.
[c] The 95% CI for difference based on Wilson Score method.
[d] P-value is based on Cochran Mantel-Haenszel test stratified by prior RBC transfusion burden (≤ 6 vs. > 6 units RBC) and IPSS risk group (low vs. intermediate-1).

The median duration of ≥ 8-week RBC TI was 51.6 weeks and the median haemoglobin (Hb) increase during the longest RBC TI period was 3.55 g/dL in imetelstat responders.

The treatment effect of imetelstat on RBC-TI ≥ 8 weeks was consistent across all clinically relevant disease characteristic subgroups, including in patients without ring sideroblasts.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rytelo in the treatment of myelodysplastic syndromes, including juvenile myelomonocytic leukaemia, in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

Imetelstat is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

In subjects with MDS receiving an intravenous infusion of 7.1 mg/kg imetelstat over 2 hours, the geometric mean (coefficient of variation [CV] %) maximum concentration ($C_{max}$) in plasma was 89.5 mcg/mL (27.3%) with peak concentrations observed at the end of the infusion. Based on $C_{max}$, imetelstat does not accumulate between treatment cycles following every four-week dosing in patients with MDS.

Distribution

Human plasma protein binding of imetelstat was 94%.

Biotransformation

Imetelstat is likely metabolised by nucleases in tissue into smaller fragments.

Elimination

The geometric mean (CV%) apparent half-life for imetelstat in plasma is approximately 4.9 hours (43.2%) in patients with MDS following a 7.1 mg/kg dose.

Linearity/non-linearity

Imetelstat plasma $AUC_{0\text{-}24h}$ increases in a more than dose proportional manner over the 0.4 to 11.0 mg/kg dose range.

Special populations
No relevant data are available for evaluation of the pharmacokinetics of imetelstat in special populations.

Among the subjects with MDS, who received imetelstat during Study MDS3001, based on liver function test (NCI-ODWG), 31 subjects had mildly abnormal liver function tests (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1× to 1.5× ULN (Grade 1) and any AST), 17 subjects had moderately abnormal liver function tests (total bilirubin > 1.5× to 3× ULN (Grade 2) and any AST)

and 2 subjects had severely abnormal liver function tests (total bilirubin > 3× ULN (Grade 3) and any AST).

Based on creatinine clearance (CrCL), 42 subjects had mild renal impairment (CrCL 60 to < 90 mL/min), 39 subjects had moderate renal impairment (CrCL 30 to < 60 mL/min), and 1 subject had severe renal impairment (CrCL 15 to < 30 mL/min).

## 5.3 Preclinical safety data

General toxicology

In 6-month mouse and 9-month monkey studies, dose-related increases in liver and kidney weights were observed. Microscopic analysis showed mild to moderate liver changes (inflammatory cell foci, increases in Kupffer cells, pigment deposition, telangiectasis) and kidney changes (mesangial thickening, glomerulonephritis/sclerosis, interstitial deposition, renal tubular haemorrhage, protein casts). These changes were fully recovered or reduced in severity after the 8- to 14-week treatment-free period. There were no significant alterations in hepatic or kidney function parameters. In these studies, the no observed adverse effect level (NOAEL) in mice and highest non-severely toxic dose (HNSTD) in monkeys were identified as the highest doses administered, which produced exposures that were up to 2.4- and 28.1-times, respectively, the human exposure at the recommended clinical dose.

Carcinogenicity

Carcinogenicity studies have not been conducted with imetelstat.

Genotoxicity

Imetelstat did not exhibit genotoxic potential in *in vitro* and *in vivo* studies.

Fertility

Assessment of effects on reproductive organs in chronic repeat-dose toxicity studies indicate the potential for impaired female fertility. Uterine endometrial atrophy was observed in monkeys administered 14.1 mg/kg once weekly for 9 months, at a mean exposure (based on AUC) that is approximately 20.0-times the human exposure at the recommended clinical dose. This effect was reversible following a 14-week recovery period.

No gross or histological changes for the male reproductive tissues were observed at any dose tested in chronic repeat-dose toxicity studies (up to 18.8 mg/kg in mice and 14.1 mg/kg in monkeys), with mean exposures (based on AUC) that are 2.4-times (mice) and 28.1-times (monkeys) the human exposure at the recommended clinical dose.

Embryo-foetal development

In embryo-foetal developmental toxicity studies, imetelstat doses of 4.7, 14.1 or 28.2 mg/kg were administered to pregnant mice and rabbits during the period of organogenesis. Imetelstat was not teratogenic, and there was no evidence of any foetal malformations in mice. Increases in fused sternebrae were noted at 28.2 mg/kg in rabbits, a dose considered to be maternally toxic based on decreases in mean gestational body weight. Embryo-lethal effects were observed at 28.2 mg/kg in both species, noted as increased post-implantation loss due to an increase in early resorptions, resulting in a decrease in viable foetuses and litter size per animal. No significant increase in post-implantation loss was observed at exposures (based on AUC) up to 1.5-times (mice) or 13.0-times (rabbits) the human exposure at the recommended clinical dose. The significance of these effects in humans is unknown.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium carbonate (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

## 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## 6.3 Shelf life

Unopened vial

4 years

Prepared solution

*Reconstituted solution*

Use immediately to prepare the diluted solution for intravenous infusion.

*Diluted solution*

Use within 48 hours when stored refrigerated at 2 ºC to 8 ºC (includes the total time from the time of reconstitution to completion of the infusion).

Use within 18 hours when stored at room temperature at 20 ºC to 25 ºC (includes the total time from the time of reconstitution to completion of the infusion).

Chemical and physical in-use stability has been demonstrated for 48 hours at 2 ºC to 8 ºC or for 18 hours at 20 ºC to 25 ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2 ºC to 8 ºC).
Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product (see section 6.3).

## 6.5 Nature and contents of container

Rytelo 47 mg powder for concentrate for solution for infusion is a clear, 8 mL Type 1 glass vial with a chlorobutyl rubber stopper and an aluminium flip-off seal with a dark green plastic cap.
Pack size: 1 vial.

Rytelo 188 mg powder for concentrate for solution for infusion is a clear, 10 mL Type 1 glass vial with a chlorobutyl rubber stopper and an aluminium flip-off seal with a royal blue plastic cap.
Pack size: 1 vial.

## 6.6 Special precautions for disposal and other handling

For single use only.

Preparation, administration and handling instructions

Rytelo is provided as a white to off-white or slightly yellow lyophilised powder for intravenous infusion only and must be reconstituted and diluted prior to administration.

*Reconstitution*

- Calculate the dose of Rytelo (total mg) based on the patient's body weight (kg):
  **Body Weight** (X kg) × **Dose** (7.1 mg/kg, unless dose reduction to 5.6 mg/kg or 4.4 mg/kg is warranted).
- Determine the number of Rytelo vials needed. More than one vial may be needed to achieve a full dose. Each Rytelo vial contains 47 mg or 188 mg.
- Remove the Rytelo vials from the refrigerator. Allow the vials to sit for 10 to 15 minutes (not to exceed 30 minutes) to warm to room temperature 20 °C to 25 °C prior to reconstitution.
- Reconstitute each vial of Rytelo according to the strength and instructions specified below:

  – *Rytelo vials containing 47 mg powder for concentrate for solution for infusion*
  Inject 1.8 mL of sodium chloride 9 mg/mL (0.9%) solution for injection directly onto the lyophilised powder for a deliverable volume of 1.5 mL. The final concentration of reconstituted solution will be 31.4 mg/mL per vial.

  – *Rytelo vials containing 188 mg powder for concentrate for solution for infusion*
  Inject 6.3 mL of sodium chloride 9 mg/mL (0.9%) solution for injection directly onto the lyophilised powder for a deliverable volume of 6.0 mL. The final concentration of reconstituted solution will be 31.4 mg/mL per vial.

  Each vial contains an overfill to account for loss of liquid during preparation and extraction of the reconstituted solution, resulting in the final concentration of 31.4 mg/mL specified above.

- Swirl each vial gently to avoid foaming until the powder is fully reconstituted (not to exceed 15 minutes). Do not shake.
- Visually inspect the reconstituted solution for particulate matter and discolouration prior to dilution. The reconstituted solution in each vial should appear as a clear to slightly hazy solution, essentially-free of visible contaminants, particles and/or particulates. Do not use if discolouration or particulate matter is present.
- Use the reconstituted solution immediately to prepare the Rytelo diluted solution in the infusion bag (see section 6.3).

*Dilution*

- Calculate the volume of reconstituted solution required for the patient based on the patient's body weight.

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{Dose}\ (7.1\ \text{mg/kg, unless dose reduction to 5.6 mg/kg or 4.4 mg/kg is warranted})}{\textbf{31.4}\ \text{mg/mL (concentration of reconstituted solution)}}$$

- To a 500 mL infusion bag of sodium chloride 9 mg/mL (0.9%) solution, add the required volume of reconstituted solution into the infusion bag. Discard any excess liquid remaining in the vial(s) which is not needed to achieve the required dose.
- Gently invert the infusion bag at least 5 times to ensure that the reconstituted solution is well-mixed. Do not shake the infusion bag prior to administration.

*Storage of diluted solution*

- Use within 48 hours when stored refrigerated at 2 ºC to 8 ºC (includes the total time from the time of reconstitution to completion of the infusion), see section 6.3.
- Use within 18 hours when stored at room temperature at 20 ºC to 25 ºC (includes the total time from the time of reconstitution to completion of the infusion), see section 6.3.

*Disposal*

- No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Geron Netherlands B.V.
Naritaweg 165
1043 BW Amsterdam
Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1894/001
EU/1/24/1894/002

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

Date of first authorisation:

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ADOH B.V.
Godfried Bomansstraat 31
6543JA Nijmegen
Netherlands

## 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.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Rytelo 47 mg powder for concentrate for solution for infusion
imetelstat

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains imetelstat sodium equivalent to 47 mg imetelstat. After reconstitution, 1 mL of solution contains 31.4 mg imetelstat.

## 3. LIST OF EXCIPIENTS

Excipients: sodium carbonate and/or hydrochloric acid (for pH-adjustment).
See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

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

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
For single use only.

## 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 a refrigerator.
Do not freeze.

## 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

Geron Netherlands B.V.
Naritaweg 165
1043BW Amsterdam
Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1894/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 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 SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rytelo 47 mg powder for concentrate
imetelstat
Intravenous use

## 2. METHOD OF ADMINISTRATION

IV use after reconstitution and dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

47 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Rytelo 188 mg powder for concentrate for solution for infusion
imetelstat

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains imetelstat sodium equivalent to 188 mg imetelstat. After reconstitution, 1 mL of solution contains 31.4 mg imetelstat.

## 3. LIST OF EXCIPIENTS

Excipients: sodium carbonate and/or hydrochloric acid (for pH-adjustment).
See package leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

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

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
For single use only.

## 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 a refrigerator.
Do not freeze.

## 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

Geron Netherlands B.V.
Naritaweg 165
1043BW Amsterdam
Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1894/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 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 SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rytelo 188 mg powder for concentrate
imetelstat
Intravenous use

## 2. METHOD OF ADMINISTRATION

IV use after reconstitution and dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

188 mg

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Rytelo 47 mg powder for concentrate for solution for infusion**
**Rytelo 188 mg powder for concentrate for solution for infusion**
imetelstat

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

**Read all of this leaflet carefully before you are given 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


1. What Rytelo is and what it is used for
2. What you need to know before you are given Rytelo
3. How you will be given Rytelo
4. Possible side effects
5. How to store Rytelo
6. Contents of the pack and other information


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

Rytelo is a medicine that contains the active substance imetelstat. Imetelstat is a type of medicine called a 'telomerase inhibitor'.

Rytelo is used in adults with anaemia (low levels of red blood cells) caused by myelodysplastic syndromes (MDS), a type of cancer. It is used to treat anaemia in patients who need red blood cell transfusions and who do not respond well to or cannot receive erythropoietin (a hormone that stimulates the production of red blood cells) based therapy.

In MDS the bone marrow does not make enough healthy blood cells and there are abnormal cells in the blood and/or bone marrow that do not develop properly. This can result in anaemia and make you feel tired or lacking energy.

Rytelo works by blocking an enzyme (protein) called 'telomerase' that helps cancer cells grow and divide. This stops the growth of abnormal cancer cells in the bone marrow and allows your bone marrow to make normal blood cells, which may make you feel less tired.

## 2. What you need to know before you are given Rytelo

**Do not take Rytelo**

- if you are allergic to imetelstat or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**

Talk to your doctor or nurse **before you are given** Rytelo if:

- you are a woman who is able to have children – see "Pregnancy and breast-feeding" and "Fertility" in section 2.
- you have recently had reactions such as bruising more easily, bleeding more than expected, nosebleeds, blood in the urine or stool, or any other signs of bleeding.
- you have signs of an infection such as fever, chills, feeling unwell, or any other sign of infection.

The conditions of bleeding, bruising or infection can worsen if certain types of your blood cells begin to decrease after you have received Rytelo – see "Serious side effects" in section 4.

To keep control of your blood cell counts and monitor you for specific side effects, your doctor or nurse will:
- do blood tests before every dose,
- do additional blood tests each week after your first two doses, and
- may give you medicines to help fight infection or make more blood cells if your blood cell counts are low.

Side effects called '**infusion-related reactions**' may happen during or soon after you are given Rytelo. These reactions can be mild to severe. To help prevent these reactions, you will be given medicines at least 30 minutes before receiving Rytelo and you will be monitored closely for at least one hour afterwards.

**Tell your doctor or nurse straight away** if you get signs of an infusion-related reaction including: low or very high blood pressure; sudden shortness of breath; lack of energy; not feeling well; headache; feeling sick (nausea); vomiting; diarrhoea; unusual heavy sweating; itchy or red skin; swelling; fever; or pain in some parts of the body (such as chest, stomach, joint, back or bone pain) – see also section 4 "Possible side effects".

**Children or adolescents**

Rytelo should not be given to children and adolescents under 18 years of age. This is because it is not known if the medicine is safe to use in this age group.

**Other medicines and Rytelo**

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

**Pregnancy and breast-feeding**

It is important that you tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby before starting Rytelo.

- **Pregnancy**
  Imetelstat **is not recommended** during pregnancy and in women who are able to have children but are not using contraception.

  Women who could become pregnant are recommended to use effective contraception (birth control) during treatment with Rytelo and for at least 1 week after the last dose. Talk with your doctor or nurse about the best contraception for you to use to avoid pregnancy. **Tell your doctor straight away** if you become pregnant or think that you are pregnant during treatment with Rytelo. Your doctor or nurse will check that you are not pregnant with a test before you start treatment.

- **Breast-feeding**
  It is unknown whether imetelstat is excreted in human milk. A risk to the breastfed child cannot be excluded. **Do not breast-feed** during treatment with Rytelo – and for 1 week after the last dose.

**Fertility**

Rytelo may reduce fertility in women. This means if you are a woman, you may find it difficult to become pregnant during or after treatment with this medicine.

**Driving and using machines**

Rytelo may have a minor influence on your ability to drive, cycle or operate tools or machines. Do not drive, cycle or operate tools or machines if you feel tired or weak or have any symptoms that may affect your ability to do these things until the symptoms have gone away – see section 4 “Possible side effects”.

**Rytelo contains sodium**

This medicine contains 35 mg sodium (main component of cooking salt) in each dose (the dose of a patient weighing 80 kg). This is equivalent to approximately 1.8 % of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How you will be given Rytelo

Rytelo will be given to you by a doctor or nurse experienced in treating blood diseases.

**How you are given Rytelo**

- The medicine is given into your vein as an infusion (drip).
- Rytelo is normally given over 2 hours.
- This medicine is given every 4 weeks.

**How much Rytelo you will be given**

The recommended dose is 7.1 mg Rytelo for each kilogram of your body weight. Your doctor will decide if the dose is right for you. Depending on how you react to the medicine your doctor may:
- interrupt and restart the infusion more slowly
- delay giving your infusion and schedule it for another day
- reduce your dose
- or stop treatment with Rytelo.

Your doctor will decide how long you are given treatment with Rytelo.

**Medicines given before Rytelo treatment**

At least 30 minutes before each dose of Rytelo, your doctor or nurse will give you medicines to help lessen the side effects caused by the infusion (infusion-related reactions) – see section 2 ”Warnings and precautions” and section 4 “Possible side effects” for more information.

**If you miss a dose**
If you miss or delay an appointment for a dose of Rytelo, it is very important to make another appointment as soon as possible. The dosing schedule will then continue to be as prescribed – every 4 weeks.

**If you are given more Rytelo than you should**

Since the infusion will be given to you by trained medical professionals in a healthcare facility, an overdose is not likely to happen. If this does happen, your doctor or nurse will check you for side effects.

## 4. Possible side effects

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

**Serious side effects**

Tell your doctor or nurse straight away if you notice any of the following signs for these serious side effects. **You may need urgent medical treatment**.

**Very common:** (may affect more than 1 in 10 people)

- Low blood levels of platelets (thrombocytopenia)
  - which may include the following symptoms: bruising more easily or bleeding more than expected, a bruise or collection of blood (haematoma), prolonged bleeding from cuts, nosebleed, blood in the gut, urine or stool or black stool.

- Low blood levels of neutrophils (neutropenia)
  - which may include the following symptoms: fever, cough, sore throat, chills, feeling unwell, or any other sign of infection.

**Common:** (may affect up to 1 in 10 people)

- Infusion-related reactions (some events starting during or after the infusion)
  - which may or may not be serious and may include one or more of the following: low or very high blood pressure; sudden shortness of breath; lack of energy; not feeling well; headache; nausea or feeling sick; vomiting; diarrhoea; unusual heavy sweating; itchy or red skin; swelling; fever; or pain in some parts of the body (such as chest, stomach, joint, back or bone pain).
- An infection in the bloodstream (sepsis)

**Other side effects**

Tell your doctor or nurse if you get any of the following side effects.

**Very common**: (may affect more than 1 in 10 people)

- decreased levels of white blood cells (leukopenia)– shown in blood tests
- weakness or a general feeling of a lack of energy or strength (asthenia)
- tiredness (fatigue)
- headache
- urinary tract infection
- increased levels of liver enzymes – shown in blood tests.

**Common**: (may affect up to 1 in 10 people)

- joint pain
- itchy skin or itchiness
- fainting
- irregular or abnormally fast heartbeat (atrial fibrillation or atrial flutter).

**Reporting of side effects**

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in

Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Rytelo

Rytelo will be stored by the healthcare professionals at the hospital or clinic. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP.
- Unopened vial: Store in a refrigerator (2 °C – 8 °C). Do not freeze.

## 6. Contents of the pack and other information

**What Rytelo contains**

- The active substance is imetelstat. Each vial contains imetelstat sodium equivalent to 47 mg or 188 mg of imetelstat. After reconstitution, each millilitre of the solution contains 31.4 mg/mL imetelstat.

- The other excipients are sodium carbonate and/or hydrochloric acid (for pH-adjustment) – see section 2, “Rytelo contains sodium”.

**What Rytelo looks like and contents of the pack**

Rytelo is a white to off-white or slightly yellow powder for concentrate for solution for infusion (powder for concentrate). Rytelo is supplied in a single dose vial containing 47 mg or 188 mg of imetelstat.

Each pack contains 1 vial.

**Marketing Authorisation Holder**
Geron Netherlands B.V.
Naritaweg 165
1043BW Amsterdam
Netherlands

**Manufacturer**
ADOH B.V.
Godfried Bomansstraat 31
6543JA Nijmegen
Netherlands

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

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**The following information is intended for healthcare professionals only:**

Do not use this medicinal product after the expiry date that is printed on the vial label and on the carton after EXP.

Preparation, administration and handling instructions

The number of vials used for a single dose will depend on the weight of the patient.

Rytelo is provided as a white to off-white or slightly yellow lyophilised powder for intravenous infusion only and must be reconstituted and diluted prior to administration.

*Premedication and monitoring for infusion-related reactions*

Premedication should be administered before any doses of Rytelo, to prevent or reduce potential infusion-related reactions. Patients should be premedicated with diphenhydramine (25 to 50 mg) and hydrocortisone (100 to 200 mg), or equivalent, at least 30 minutes before dosing with Rytelo.

Patients should be monitored for adverse reactions for at least one hour after the infusion has been completed. See SmPC sections 4.2 and 4.4 for management of symptoms.

*Reconstitution*

- Calculate the dose of Rytelo (total mg) based on the patient's body weight (kg):
  **Body Weight** (X kg) × **Dose** (7.1 mg/kg, unless dose reduction to 5.6 mg/kg or 4.4 mg/kg is warranted).
- Determine the number of Rytelo vials needed. More than one vial may be needed to achieve a full dose. Each Rytelo vial contains 47 mg or 188 mg.
- Remove the Rytelo vials from the refrigerator. Allow the vials to sit for 10 to 15 minutes (not to exceed 30 minutes) to warm to room temperature 20 °C to 25 °C prior to reconstitution.
- Reconstitute each vial of Rytelo according to the strength and instructions specified below:

  – *Rytelo vials containing 47 mg powder for concentrate for solution for infusion*
  Inject 1.8 mL of sodium chloride 9 mg/mL (0.9%) solution for injection directly onto the lyophilised powder for a deliverable volume of 1.5 mL. The final concentration of reconstituted solution will be 31.4 mg/mL per vial.

  – *Rytelo vials containing 188 mg powder for concentrate for solution for infusion*
  Inject 6.3 mL of sodium chloride 9 mg/mL (0.9%) solution for injection directly onto the lyophilised powder for a deliverable volume of 6.0 mL. The final concentration of reconstituted solution will be 31.4 mg/mL per vial.

  Each vial contains an overfill to account for loss of liquid during preparation and extraction of the reconstituted solution, resulting in the final concentration of 31.4 mg/mL specified above.

- Swirl each vial gently to avoid foaming until the powder is fully reconstituted (not to exceed 15 minutes). Do not shake.
- Visually inspect the reconstituted solution for particulate matter and discolouration prior to dilution. The reconstituted solution in each vial should appear as a clear to slightly hazy solution, essentially-free of visible contaminants, particles and/or particulates. Do not use if discolouration or particulate matter is present.
- Use the reconstituted solution immediately to prepare the Rytelo diluted solution in the infusion bag.

*Dilution*

- Calculate the volume of reconstituted solution required for the patient based on the patient's body weight.

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{Dose}\ (7.1\ \text{mg/kg, unless dose reduction to } 5.6\ \text{mg/kg or } 4.4\ \text{mg/kg is warranted})}{\textbf{31.4}\ \text{mg/mL (concentration of reconstituted solution)}}$$

- To a 500 mL infusion bag of sodium chloride 9 mg/mL (0.9%) solution, add the required volume of reconstituted solution into the infusion bag. Discard any excess liquid remaining in the vial(s) which is not needed to achieve the required dose.
- Gently invert the infusion bag at least 5 times to ensure that the reconstituted solution is well-mixed. Do not shake the infusion bag prior to administration.

*Storage of diluted solution*

- Use within 48 hours when stored refrigerated at 2 ºC to 8 ºC (includes the total time from the time of reconstitution to completion of the infusion).
- Use within 18 hours when stored at room temperature at 20 ºC to 25 ºC (includes the total time from the time of reconstitution to completion of the infusion).
- Chemical and physical in-use stability has been demonstrated for 48 hours at 2 ºC to 8 ºC or for 18 hours at 20 ºC to 25 ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 ºC to 8 ºC, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

*Method of administration*

- Administer the diluted solution as an intravenous infusion over 2 hours (i.e. 250 mL/h). Do not administer as an intravenous push or bolus.

- For reduced infusion rates that may be necessary due to infusion-related reactions, see below and refer to section 4.2, Table 3, of the SmPC.

**Rate administration modifications for infusion-related reactions**

| **Adverse reaction** | **Severity grade**[a] | **Occurrence** | **Treatment modification** |
|---|---|---|---|
| **Infusion-related reactions** (see SmPC sections 4.4 and 4.8) | Grade 2 or 3 | First and second | • Interrupt the infusion until resolution or the intensity of the adverse reactions decrease to Grade 1[a]<br>• Restart infusion at 50% of the infusion rate administered prior to the adverse reactions (i.e., 125 mL/h) |

Grade 1: mild; Grade 2: moderate; Grade 3: severe

*Disposal*

- No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.