Sikkerhetsinformasjon ! Etter krav fra Direktoratet for medisinske produkter

A healthcare professional's guide to minimizing risks with ▼Zolgensma® (onasemnogene abeparvovec)

This brochure has been developed to support healthcare professionals expected to prescribe, dispense and administer Zolgensma. The brochure aims to provide guidance on key safety areas related to hepatotoxicity and thrombotic microangiopathy with Zolgensma and to help mitigate possible risks before, during and after treatment. The brochure should be read along with the Summary of Product Characteristics (SmPC).

Zolgensma is indicated for the treatment of:

- Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron 1 (*SMN1*) gene and a clinical diagnosis of SMA Type 1, or
- Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene

Zolgensma treatment should be administered in clinical centers and supervised by a physician experienced in the management of patients with SMA.

▼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.

Healthcare professionals are requested to report any novel, unexpected, and serious suspected adverse reactions/events through the electronic form: www.dmp.no/meldeskjema.

If you have any questions or concerns about Zolgensma, speak to your Novartis representative.

SMA, spinal muscular atrophy; SMN, survival motor neuron; SmPC, Summary of Product Characteristics.

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Thank you for taking the time to read this guide. This document has been developed to help mitigate possible risks before the start of Zolgensma treatment, at the time of the infusion, and after infusion by providing a guide focusing on the following safety areas of concern:

- **Hepatotoxicity**
- **Thrombotic microangiopathy**

If you have any questions or concerns about this medicine, please refer to the SmPC or speak to your Novartis representative.

Useful contacts

SmPC, Summary of Product Characteristics.

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What is in this guide?

Understanding the possible risks of Zolgensma

Important safety information

Important identified risks following Zolgensma treatment are outlined below. Please refer to the SmPC for full safety and prescribing information, as other warnings and precautions are in place for Zolgensma.

Hepatotoxicity

Immune-mediated hepatotoxicity following Zolgensma treatment is generally manifested as elevated alanine transaminase (ALT) and/or aspartate aminotransferase (AST) levels.

Acute serious liver injury and acute liver failure, including fatal cases, have been reported after treatment with Zolgensma. This occurs typically within 2 months after treatment and despite receiving corticosteroids before and after infusion.

Hepatotoxicity may require adjustment of the immunomodulatory regimen including longer duration, increased dose or prolongation of the corticosteroid taper.

Thrombotic microangiopathy

Zolgensma may increase the risk of thrombotic microangiopathy (TMA), generally within the first 2 weeks after treatment.

TMA is an acute and life-threatening condition, characterized by thrombocytopenia, microangiopathic hemolytic anemia and acute kidney injury. Fatal outcomes have been observed with Zolgensma treatment. Concurrent immune system activation (e.g. from infections, vaccinations) have also been reported as possible triggers.

If patients show clinical signs, symptoms or laboratory findings consistent with TMA, a specialist should be consulted immediately to manage TMA as clinically indicated.

Please refer to section 4.4 of the SmPC for further information on warnings and precautions for use of Zolgensma

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SmPC, Summary of Product Characteristics; TMA, thrombotic microangiopathy.

Additional warnings and precautions associated with Zolgensma include, but are not limited to:

- **Thrombocytopenia**
  - Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in Zolgensma clinical studies
- **Elevated Troponin-I**
  - Increases in cardiac troponin-I levels following Zolgensma infusion have been observed

Please note that additional warnings and precautions associated with Zolgensma are not limited to those identified in this guide. Please refer to the SmPC or your Novartis representative for full safety information for Zolgensma.

SmPC, Summary of Product Characteristics.

Mitigating possible risks with Zolgensma

1. Before the start of treatment

Inform the caregiver(s) about the main risks associated with Zolgensma and their signs and symptoms, including but not limited to TMA, hepatic failure and thrombocytopenia.

Blood tests

Anti-adeno-associated virus serotype 9 (AAV9) antibody formation can take place after natural exposure.

Patients should be tested for the presence of AAV9 antibodies prior to treatment using an appropriately validated assay.

It is not yet known whether or under what conditions Zolgensma can be safely and effectively administered in the presence of AAV9 antibodies above 1:50. Re-testing may be performed if AAV9 antibody titres are reported as above 1:50.

Before administration of Zolgensma, baseline laboratory testing is also required for, but not limited to:

- Liver function: ALT, AST, total bilirubin, albumin, prothrombin time, partial thromboplastin time (PTT), and international normalized ratio (INR)
- Creatinine
- Complete blood count (including hemoglobin and platelet count)
- Troponin-I

Regular blood tests are required for at least 3 months following Zolgensma infusion. Please refer to pages 16–18 of this brochure for a detailed blood test schedule.

AAV9, adeno-associated virus serotype 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PTT, partial thromboplastin time; TMA, thrombotic microangiopathy.

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Inform the caregiver(s) about the need for regular blood sampling.

Caregivers must be advised that blood tests will be required for at least 3 months following Zolgensma treatment. Compliance with the monitoring blood test schedule is important for best patient outcomes. Blood test appointment dates and times should be agreed upon and booked prior to treatment.

Corticosteroid dosing

An immune response to the AAV9 capsid will occur after Zolgensma administration leading to:

elevations in liver aminotransferases

elevations of troponin-I

decreased platelet count

To dampen the immune response, immunomodulation with corticosteroids is recommended

24 hours prior to Zolgensma infusion, it is recommended to initiate a corticosteroid regimen. The following initial prescription is recommended:

Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used.)

Inform caregiver(s) about the importance of corticosteroid medication.

Inform the caregiver on the urgency to make you aware of any event of vomiting, to ensure the patient does not miss corticosteroid dosing.

AAV9, adeno-associated virus serotype 9.

Mitigating possible risks with Zolgensma

1. Before the start of treatment *(continued)*

Overall health

Due to the increased risk of serious systemic immune response, it is recommended that patients are clinically stable in their overall health status, including hydration and nutritional status and absence of infection.

Inform caregiver(s) of the need for increased vigilance in the prevention, monitoring, and management of infection before and after Zolgensma infusion.

The caregiver must:

- Be informed of the signs and symptoms suggestive of infection. If the patient shows any signs and symptoms, they must contact you urgently
- Help to prevent infections by avoiding situations that may increase the risk of the patient getting infections, such as practicing good hand hygiene, good coughing/sneezing etiquette, and limiting potential contacts
- Be informed about the possible infection risk as part of circumcision and recommend performing circumcision at a medical setting to minimize the risk for infections

In case of acute or chronic uncontrolled active infections, treatment should be postponed until the infection has resolved and the patient is clinically stable.

Vaccination schedule

Before the start of treatment the patient's vaccination schedule should be evaluated.

Where feasible, the vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following Zolgensma infusion.

Seasonal respiratory syncytial virus (RSV) prophylaxis is recommended and should be up to date. Live vaccines, such as measles, mumps and rubella (MMR) and varicella, should not be administered to patients on an immunosuppressive steroid dose.

Weight

Patients will receive a dose of nominal 1.1 x 10^{14} vg/kg Zolgensma. The total volume of Zolgensma that the patient will receive is determined by their weight. The patient must be weighed prior to treatment to ensure that they receive the correct dose.

MMR, measles, mumps and rubella; RSV, respiratory syncytial virus.

Mitigating possible risks with Zolgensma

2. At the time of infusion

Overall health

Check the overall health status of the patient is suitable for infusion (e.g. resolution of infections) or if a postponement is warranted.

Treatment should not be initiated concurrently to active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B), until the infection has resolved. If the patient shows any signs or symptoms suggestive of infection, treatment must be postponed.

In case of acute or chronic uncontrolled active infections, treatment should be postponed until the infection has resolved and the patient is clinically stable.

Patient weight

Zolgensma dosing is weight-based.

If there is a delay between ordering Zolgensma and infusion, the patient may need to be re-weighed to ensure accuracy of Zolgensma dose.

Contact Novartis immediately if you are concerned about a change in the patient's weight since ordering the patient's dose of Zolgensma.

Corticosteroid dosing

Check if corticosteroid treatment was started 24 hours before the infusion of Zolgensma.

To dampen the immune response, the patient should have started their immunomodulatory regimen with corticosteroids, with the first dose given 24 hours prior to Zolgensma treatment. On the day of Zolgensma treatment, the patient should continue the regimen and receive the following dose of corticosteroid:

Prednisolone orally 1 mg/kg/day (or equivalent if another corticosteroid is used).

The immunomodulatory regimen should be continued for 30 days (including the day of administration of Zolgensma), followed by a minimum 28 day taper period. Please refer to page 13 for corticosteroid dosing following infusion.

Mitigating possible risks with Zolgensma

2. At the time of infusion *(continued)*

Zolgensma infusion

Zolgensma is for single-dose intravenous infusion only.

Zolgensma should be administered with the syringe pump as a single, slow infusion of approximately 60 minutes. Insertion of a secondary 'back-up' catheter is recommended.

It should be administered as intravenous infusion only. **Do not administer by intravenous push or bolus.**

Following completion of infusion, the line should be flushed with saline.

Please see section 4.2 of the SmPC for important information on dosing and administration of Zolgensma.

Zolgensma contains genetically-modified organisms. You should therefore take the appropriate precautions when handling or administering Zolgensma.

For detailed instructions on the preparation, handling, accidental exposure and disposal (including proper handling of bodily waste) of Zolgensma, refer to the SmPC.

SmPC, Summary of Product Characteristics.

3. After infusion

Corticosteroid dosing after Zolgensma

Corticosteroid treatment should continue for at least 2 months; and not be tapered until AST/ALT are less than 2 x upper limit of normal (ULN), and all other assessments, e.g. total bilirubin, return to normal range.

This period may need to be prolonged if the patient's liver enzymes do not decrease quickly enough, until they decrease to an acceptable level. The dose of corticosteroid given to the patient should be slowly reduced at this time until treatment can be fully stopped.

Prednisolone 1 mg/kg/day should be given orally (or equivalent if another corticosteroid is used) for 30 days including the day of administration of Zolgensma. At the end of this 30-day period of corticosteroid regimen, patients should have their liver function checked.

For patients with unremarkable findings (normal clinical exam, total bilirubin, and whose ALT and AST values are both below 2 x ULN at the end of the total 30-day period):

Gradually taper prednisolone (or equivalent) over 28 days

- For example: 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day oral prednisolone

For patients with liver function abnormalities at the end of the total 30-day period:

Continue with prednisolone until the AST and ALT values are below 2 x ULN and all other assessments return to normal range, followed by tapering over 28 days or longer if needed.

If at any time patients do not respond adequately to the equivalent of 1 mg/ kg/day oral prednisolone, based on the patient's clinical course, prompt consultation with a pediatric gastroenterologist or hepatologist and adjustment to the recommended immunomodulatory regimen, including increased dose, longer duration or prolongation of corticosteroid taper, should be considered.

ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

Mitigating possible risks with Zolgensma

3. After infusion *(continued)*

Regular blood tests

Close and regular monitoring (clinical and laboratory) of the individual patient course should be performed for at least 3 months following Zolgensma infusion.

Liver function (ALT, AST, total bilirubin) should be monitored at regular intervals for at least 3 months following infusion with Zolgensma.

Tests should be conducted:
- Weekly in the first month and during the entire corticosteroid taper period
- Every 2 weeks for another month
- At other times as clinically indicated

Patients with worsening liver function test results and/or signs or symptoms of acute illness should be promptly assessed and monitored closely.

If patients do not respond to corticosteroids, or if liver injury is suspected, consult a pediatric gastroenterologist or hepatologist.

Platelet counts should be closely monitored within the first 3 weeks following infusion and on a regular basis afterwards.

After Zolgensma treatment, platelet counts should be monitored:
- At least weekly for the first month
- Every other week for the second and third months until platelet counts return to baseline

If TMA is suspected, a specialist should be consulted.

Troponin-I levels should be monitored for at least 3 months following Zolgensma infusion or until levels return to within normal reference range for patients with SMA.

Consider consultation with a cardiac expert as needed.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SMA, spinal muscular atrophy; TMA, thrombotic microangiopathy.

Temporary shedding

Temporary shedding of Zolgensma may occur, primarily through bodily waste, for at least 1 month after treatment with Zolgensma.

Provide the caregiver with practical advice concerning bodily waste disposal to be followed for at least 1 month after their child's treatment with Zolgensma.

Wear protective gloves when coming into contact with bodily fluids or waste.

Wash hands thoroughly afterwards with soap and warm running water, or an alcohol-based hand sanitizer.

Use double plastic bags to dispose of soiled diapers and other waste. Disposable diapers may still be disposed of in household waste.

Blood test schedule

Month 1 after Zolgensma treatment (30 days)

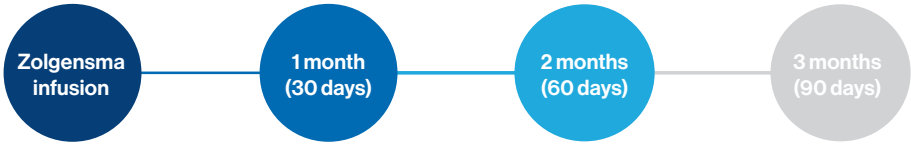
Blood tests

For the first month following Zolgensma treatment, your patient will require **weekly blood tests for liver function and blood-platelet count**. Troponin-I levels should be monitored for at least 3 months following Zolgensma infusion or until levels return to within normal reference range for patients with SMA. The table below can be used to guide you on the blood test schedule.

Number of weeks after Zolgensma treatment	Blood tests
Troponin-I (if levels have not returned to within normal reference range for patients with SMA)	
Week 1	Liver function Platelet count
Week 2	Liver function Platelet count
Week 3	Liver function Platelet count
Week 4	Liver function Platelet count

SMA, spinal muscular atrophy.

Month 2 after Zolgensma treatment (60 days)



Blood tests

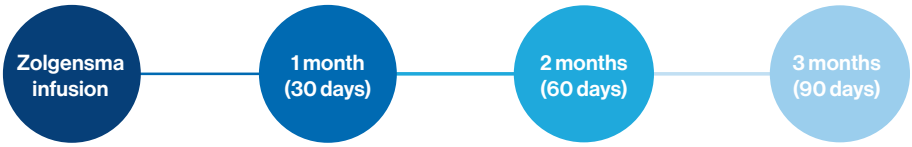
For the second month following Zolgensma treatment and during the entire corticosteroid taper period, your patient will require **weekly blood tests for liver function. Blood-platelet count should be monitored every other week** until count returns to baseline. Troponin-I levels should be monitored for at least 3 months following Zolgensma infusion or until levels return to within normal reference range for patients with SMA. The table below can be used to guide you on the blood test schedule.

Number of weeks after Zolgensma treatment	Blood tests
Troponin-I (if levels have not returned to within normal reference range for patients with SMA)	
Week 5	Liver function
Week 6	Liver function Platelet count (if not returned to baseline)
Week 7	Liver function
Week 8	Liver function Platelet count (if not returned to baseline)

SMA, spinal muscular atrophy.

Blood test schedule

Month 3 after Zolgensma treatment (90 days)



Blood tests

In the third month following Zolgensma treatment, your patient will require **regular blood tests for liver function and blood-platelet count** (until platelet counts return to baseline). Troponin-I levels should be monitored for at least 3 months following Zolgensma infusion or until levels return to within normal reference range for patients with SMA. The table below can be used to guide you on the blood test schedule.

Number of weeks after Zolgensma treatment	Blood tests
Troponin-I (if levels have not returned to within normal reference range for patients with SMA)	
Week 9	Liver function (for a patient whose liver function does not return to baseline after treatment, or for a patient that is at the corticosteroid tapering period)
Week 10	Liver function Platelet count (if not returned to baseline)
Week 11	Liver function (for a patient whose liver function does not return to baseline after treatment, or for a patient that is at the corticosteroid tapering period)
Week 12	Liver function Platelet count (if not returned to baseline)

During and after month 3, further blood tests and monitoring may be required in certain instances, which are outlined below.

- Liver function should continue to be monitored weekly through the end of corticosteroid tapering and at other times as clinically indicated
- Platelet counts should continue to be monitored every 2 weeks until they return to baseline
- Troponin-I levels should be monitored until levels return to within the normal reference range for patients with SMA

Summary checklist

The below checklist is a summary of actions to take before the start, at the time of, and after Zolgensma infusion, to help mitigate possible risks associated with Zolgensma treatment:

Before the start of treatment

- ☐ **Inform the caregiver about the:**
  - ☐ **Main risks with Zolgensma and their signs and symptoms, including TMA, hepatic failure and thrombocytopenia**
  - ☐ **Practical advice concerning bodily waste disposal**
  - ☐ **Need for regular blood sampling**
  - ☐ **Importance of corticosteroid medication**
  - ☐ **Need for increased vigilance in the prevention, monitoring, and management of infection before and after Zolgensma treatment**
- ☐ **Take blood tests, including testing for the presence of AAV9 antibodies** to establish baseline levels
- ☐ **Give corticosteroid dose** to dampen the immune response
- ☐ **Evaluate vaccination schedule** to decide whether it needs to be adjusted
- ☐ **Check overall health,** as treatment must be postponed in the event of signs or symptoms suggestive of infection
- ☐ **Check patient weight** to ensure the patient receives the correct dose of Zolgensma

At the time of infusion

- ☐ **Check overall health status** of the patient is suitable for the infusion (e.g. resolution of infections) or if a postponement is warranted
- ☐ **Check corticosteroid dose was started 24 hours before the infusion of Zolgensma** and provide next dose to dampen the immune response
- ☐ **Check patient weight** to ensure the patient receives the correct dose of Zolgensma
- ☐ **Zolgensma infusion** is given once only
- ☐ **Appropriate Zolgensma handling** must be followed

After infusion

- ☐ **Corticosteroid treatment should continue for at least 2 months; and not be tapered until AST/ALT are less than 2 x ULN, and all other assessments, e.g. bilirubin, return to a normal range**
- ☐ **Close and regular monitoring (clinical and laboratory) of the individual patient course should be performed for at least 3 months**
- ☐ **Prompt assessment of patients with worsening liver function tests and/or signs or symptoms of acute illness**
- ☐ **If patients do not respond adequately to corticosteroids, or if liver injury is suspected, consultation with a pediatric gastroenterologist or hepatologist is required**
- ☐ **If TMA is suspected, a specialist should be consulted**

Please refer to the SmPC for full safety and prescribing indications as other warnings and precautions are in place for Zolgensma.

AAV9, adeno associated-virus serotype 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SmPC, Summary of Product Characteristics; TMA, thrombotic microangiopathy; ULN, upper limit of normal.

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Rapportering av bivirkninger

▼Zolgensma er underlagt særlig overvåking for å oppdage ny sikkerhetsinformasjon så raskt som mulig.

Helsepersonell bes melde nye, uventede og alvorlige mistenkte bivirkninger på elektronisk meldeskjema: **www.dmp.no/meldeskjema**

Tilgang til opplæringsmateriell

Oppdatert preparatomtale (SPC) og opplæringsmateriell er tilgjengeling på **www.felleskatalogen.no** under Zolgensma.

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