

## Mebendazole and fever

### Introduction

Mebendazole is an anthelmintic and is indicated *for the treatment of infections by the following worms: Enterobius vermicularis (pinworm), Ascaris lumbricoides (common roundworm), Trichuris trichiuria (whipworm) and Ancylostoma duodenale (common hookworm) and Necator americanus (American hookworm)*. Mebendazole interferes with the cellular tubulin polymerization in the intestine of the worm by specifically binding to tubulin, which leads to degenerative alterations in the tegument and intestinal cells of the worm. This disrupts the worm's glucose absorption and digestive functions to such an extent that an autolytic process is initiated [1].

Fever, or pyrexia, is a common complaint and can have many causes. An increase in body temperature is often due to a physiological process brought on by infectious causes or non-infectious causes, such as inflammation, malignancy, autoimmune processes or drug reactions. The normal temperature of a human body is approximately 37 degrees Celsius [2,3].

### Reports

In the period from September 1<sup>st</sup> 1997 until April 4<sup>th</sup> 2024 the Netherlands Pharmacovigilance Centre Lareb received 23 reports of fever in association with the use of mebendazole. Table 1 provides a detailed overview of the 23 cases of fever reported for mebendazole [4]. At Lareb the following categories to code the reported fever based on measured body temperature are used: body temperature increased (37,5-38 degrees Celsius), pyrexia (38,1-40,5 degrees Celsius), hyperpyrexia (40,6-42 degrees Celsius) and hyperthermia (>42 degrees Celsius). The term 'fever' was coded when no specific body temperature was reported.

Table 1. Fever cases reported after use of mebendazole.

Worldwide Case ID, primary source, sex, age, concomitant medication	Suspect, IA drug, dosage, indication	Reported ADRs	Latency after start, Outcome, Duration
A. NL-LRB-00963564, Consumer or other non health professional, male, 7-10 Years, none	Mebendazole, 100 milligram, Enterobiasis	Red spotty rash Fever Nausea Headache	1 day, Not recovered, -
B. NL-LRB-00947359, Consumer or other non health professional, female, 2-4 years, none	Mebendazole, 100 milligram, Enterobiasis	Fever	3 hours, Recovering, -
C. NL-LRB-00946319, Consumer or other non health professional, female, 4-7years Months, none	Mebendazole, 100 milligram / 2 Weeks, Drug use for unknown indication	Fever Abdominal pain Headache Listless	1 day, Unknown, -

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D. NL-LRB-00944381, Consumer or other non health professional, female, 10-20 Years, none	Mebendazole,  100 milligram / 1 Days,  Worms	Fever Chills Feeling hot and cold	2 days,  Not recovered,  -
E. NL-LRB-00903669, Consumer or other non health professional, male, 2-4 years, none	Mebendazole 100 milligram / 1 Days, Pinworms	Abdominal pain Fever	1 day,  Not recovered,  -
F. NL-LRB-00903121, Consumer or other non health professional, male, 2-4 years, none	Mebendazole  100 milligram Enterobiasis	Pyrexia	1 hour,  Recovered,  12 hours
G. NL-LRB-00886077, Consumer or other non health professional, female, 4-7 years, none	Mebendazole,  100 milligram / 1 Days, Worms	Pyrexia Fatigue	5 hours,  Not recovered,  -
H. NL-LRB-00793156, Consumer or other non health professional, female, 2-4 years, none	Mebendazole,  100 milligram / 1 Days, Worms	Fever Diarrhoea Cold hands & feet	2 days,  Not recovered,  -
I. NL-LRB-00771784, Other health professional, female, 4-7 years months, none	Mebendazole  100 milligram / 1 Days Worms	Abdominal pain Diarrhoea Vomiting projectile Fever	6 days,  Recovering,  1 day
J. NL-LRB-00396913, Consumer or other non health professional, male, 7-10 Years, none	Mebendazole  100 milligram, Threadworm infection	Abdominal cramps Body temperature increased	Within 1 day,  Unknown,  -
K. NL-LRB-00378561, Consumer or other non health professional, male, 4-7 Years, none	Mebendazole,  100 milligram / 2 Weeks, Enterobiasis	Fever Abdominal pain Malaise	1 day,  Recovering,  -
L. NL-LRB-00360180, Consumer or other non health professional, female, 1-2 years, none	Mebendazole,  100 milligram total,  Worms	Urticaria Fever Eczema	10 hours,  Recovering,  -

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M. NL-LRB-00355051, Consumer or other non health professional, female, 30-40 Years, none	Mebendazole,  100 milligram total, Worms	Stomatitis aphthous Fever	6 days,  Recovered, -
N. NL-LRB-00356890, Consumer or other non health professional, female, 50-60 Years, none	Mebendazole,  100 milligram / 2 Weeks, Worms	Abdominal pain Diarrhoea Fever Dizziness	2 days,  Unknown, -
O. NL-LRB-00320354, Consumer or other non health professional, female, 4-7 years,  none	Mebendazole,  100 milligram / 2 Weeks,  Worms	Abdominal pain Fever Faeces discoloured	24 hours,  Recovering -
P. NL-LRB-238416, Consumer or other non health professional, female, 2-4 years, none	Mebendazole,  100 milligram / 1 Weeks, Infection parasitic	Pyrexia Convulsion febrile	2 days,  Recovering, -
Q. NL-LRB-215625, Consumer or other non health professional, female, 2-4 Years, none	Mebendazole,  100 milligram / 2 Weeks,  Parasitic infection NOS	Pyrexia	5 hours,  Unknown, -
R. NL-LRB-215422, Physician, female, 1-2 Years, none	Mebendazole,  100 milligram / 1 Days,  Infection parasitic	Maculo papular rash Pyrexia	1 day,  Recovered,  1 day
S. NL-LRB-155783, Pharmacist, male, 2-4 Years, none	Mebendazole,  100 milligram / 14 Days  Drug use for unknown indication	Dyspnoea Pyrexia Swelling face	35 hours,  Recovered,  3 days
T. NL-LRB-88329, Pharmacist, female, 2-4 years, none	Mebendazole,  100 milligram  Drug use for unknown indication	Body temperature increased	5 hours,  Recovered,  -
U. NL-LRB-81392, Physician, male, 40-50 Years, none	Mebendazole (Vermox),  100 milligram , Helminth infection, unspecified	Pyrexia Headache Myalgia	2 hours,  Recovered,  1 day

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V. NL-LRB-29131, Physician, female, 2-4 Years, none	Mebendazole  100 milligram / 1 Days, Helminth infection, unspecified	Fever Hallucination	7 hours,  Unknown,  -
W. NL-LRB-18595, Pharmacist, female, 7-10 Years, none	Mebendazole  100 milligram / 2 dosage form / Total, Intestinal parasitism, unspecified	Headache Fever	1 day,  Unknown,  -

### Detailed description of the reports

Report I: For this indication the patient needed to take mebendazole twice, two weeks apart. The patient developed the same reaction with the same latency time after start after both uses.

Report K: For this indication the patient needed to take mebendazole twice, two weeks apart. The patient developed the same reaction with the same latency time after start after both uses.

Report P: The patient experienced pyrexia of 40 degrees Celsius which led to a febrile convulsion after two days.

Report S: The patient developed severe dyspnea, high fever and a swollen face 1,5 days after use of mebendazole. The patient was seen by a doctor, but no cause of the symptoms was found. The complaints recovered over a period of 3 days. Patient was advised to not take the second administration of mebendazole.

### Other sources of information

#### SmPC

In the Dutch SmPC of mebendazole, fever is not reported as an adverse drug reaction.[1] Fever is only described in the Dutch patient leaflet as a symptom of adverse drug reactions of the skin, such as Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [5].

In the Dutch SmPC of albendazole, which is also an anthelmintic with the same mechanism of action as mebendazole, fever is mentioned as an adverse drug reaction [6].

#### Other sources

The Dutch children's formulary (Kinderformularium) described that in infants, fever which can lead to febrile convulsion, is a known ADR of mebendazole.[7]

In product information sources of other countries fever is described as a well-known (rare) ADR of Vermox®/mebendazole [8,9,10].

#### Databases

Table 2: Reports of pyrexia associated with mebendazole in the Lareb, Eudravigilance and WHO database [4,11,12].

Database	Number of reports	ROR (95% CI)
Lareb	23	1.0 (0.6 - 1.5)
Eudravigilance	68	0.7 (0.6-0.90)
Vigibase	131	0.5 (0.4-0.6)

In the WHO global database Vigibase, a total of 131 pyrexia cases associated with mebendazole were reported as of July 17<sup>th</sup> 2024. This association was not disproportional, with an IC<sub>025</sub> of -1,3 and a ROR<sub>025</sub> of 0,4 (number of cases in background 39.171.100) [11].

#### Literature

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There is little known about the occurrence of fever in relation to the use of mebendazole. Some cases of fever after mebendazole use were reported, particularly in those receiving high-dose therapy for extraintestinal infections [13,14,15]. Fever may have been related to drug-induced tissue necrosis of hydatid cysts in two patients [14] or due to an idiosyncratic reaction in one patient [15].

### Mechanism

For various antihelminthic drugs it has been described that an inflammatory response termed the Mazzotti reaction (itching, rash, fever, swollen lymph nodes, and arthralgias) may occur as the worms are eliminated. Although a full-blown Mazzotti reaction has not been described for mebendazole, a reaction to elimination of intestinal worms is possible [16,17].

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 23 reports of fever in association with the use of mebendazole. Fever is only mentioned in the SmPC as a symptom of agranulocytosis or reactions on the skin (SJS or TEN), but in all but one of the cases reported to Lareb there were no other causes for fever reported. Fever occurred with a median latency of 1 day after use of mebendazole and half of the patients are recovering or recovered at time of reporting. Only two patients were treated with paracetamol. Other possible causes for pyrexia such as an infection are not mentioned in the reports, but cannot be excluded. Fever is described in different sources from other countries as well as in the SmPC of albendazole. Based on the reports received by Lareb, the relation between mebendazole and pyrexia is deemed plausible.

### References

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