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ORIGINAL ARTICLE

Metamizole-induced agranulocytosis: utilisation trends, pharmacovigilance signals and regulatory risk-minimisation in Switzerland

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Summary

INTRODUCTION: The therapeutic role of metamizole (dipyrone) remains controversial because of the risk of metamizole-induced agranulocytosis, a very rare, idiosyncratic, life-threatening adverse reaction. We described utilisation, spontaneous reporting and recent regulatory actions in Switzerland.

METHODS: We estimated national metamizole utilisation as defined daily doses (DDD; WHO DDD 3 g/day) for 2014–2023, derived from aggregated national sales data; individual case safety reports (ICSR) of metamizole-induced agranulocytosis were retrieved from VigiBase (the WHO global safety database) for 2014–2024. Outputs included annual counts, fatal proportion and utilisation-normalised reporting (metamizole-induced agranulocytosis per million DDD); analyses were primarily descriptive.

RESULTS: Utilisation increased by ~79% during the analysed period with a formulation mix of 95.7% oral, 4.2% ampoules, 0.1% suppositories. Metamizole-induced agranulocytosis reports rose from 13 (2014) to 57 (2024), with year-to-year variability; the fatal proportion declined from 13.5% (2014–2018; 17/126) to 5.8% (2019–2023; 13/224) and 1.8% in 2024 (1/57). Utilisation-normalised reporting increased from 1.42 to 3.29 per million DDD (total), while fatal reports remained low and trended downward (mean 0.249 per million DDD, 2014–2023). Among Swiss fatal cases, methotrexate was co-reported as a concomitant drug in 39.5% (15/38) (extended fatal set 2011–2025; fatal ICSRs irrespective of onset year). Switzerland contributes a disproportionately high absolute number of cumulative metamizole-induced agranulocytosis reports.

REGULATORY ACTIONS: EMA and Swissmedic implemented strengthened warnings; Swissmedic additionally required a red-framed outer carton statement, clarified indications (second-line severe pain; refractory high fever) and advised avoiding concomitant methotrexate; a Direct Healthcare Professional Communication was issued.

CONCLUSION: Regulatory assessments by EMA and Swissmedic concluded that the benefits of metamizole continue to outweigh the risks, provided the drug is used appropriately, action is taken promptly at first symptoms and concomitant methotrexate is avoided. However, the number of reported cases of agranulocytosis underscores the known risk in the context of widespread use. Spontaneous reports reflect reporting intensity, not incidence; ongoing monitoring of risk-minimisation effectiveness is warranted.

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Introduction

Metamizole (dipyrone), first marketed in 1922 [1], is converted to its active metabolite 4-methylaminoantipyrine (4-MAA) [2]. It provides analgesic, antipyretic and spasmolytic effects and is an inducer of hepatic enzymes, which is relevant for drug–drug interactions in older patients with polypharmacy [3].

Metamizole is widely used in several countries, including Germany, Spain and Switzerland, but is banned in others – including the United States, Canada, the United Kingdom, Australia, France, Norway, Sweden and Japan – primarily due to concerns about agranulocytosis [4]. In Swit-

zerland, utilisation has increased over the last decade, with marked regional heterogeneity and higher use among older patients when non-steroidal anti-inflammatory drugs (NSAID) are contraindicated [5].

Metamizole-induced agranulocytosis is a very rare, idiosyncratic, potentially fatal adverse reaction. It can occur at any time during treatment or shortly after discontinuation, is dose-independent and may arise even after uneventful prior use. Metamizole-induced agranulocytosis is characterised by abrupt, severe neutropenia with a high risk of infection, sepsis and death if not promptly recognised and treated.

Case example: Fatal metamizole-induced agranulocytosis. – This case was reported to Swissmedic as an individual case safety report (ICSR): An adult patient had been taking metamizole for several weeks to manage musculoskeletal pain. A few days after discontinuation, the patient presented to a primary care physician with symptoms including headache, sore throat and cold sweats. During the consultation, he suffered a cardiac arrest and was immediately resuscitated. Following initial stabilisation in hospital, investigations revealed severely reduced left ventricular ejection fraction (LVEF), right heart strain and no significant coronary artery disease. Laboratory findings indicated elevated inflammatory markers, impaired liver and kidney function and haematological aplasia. Further diagnostics revealed bilateral pulmonary infiltrates, left-sided otitis externa and a coated right tonsil. Despite intensive medical intervention, the patient progressed to septic shock and died the following day.

The affected blood cell lineages can decline within 24 hours. Early symptoms are non-specific (sore throat, fatigue, mucosal ulcers, with or without fever) and may be masked when metamizole is taken for febrile illness or together with antibiotics. At the first signs of infection or mucosal symptoms, metamizole must be stopped immediately and an urgent full blood count with differential obtained. Re-exposure is strictly contraindicated.

The reported incidence of metamizole-induced agranulocytosis varies by study design and population [6]. In a German statutory health insurance analysis, the reported risk of drug-induced agranulocytosis/neutropenia after metamizole prescription was 1:1602 [7]. This estimate likely overstates metamizole-induced agranulocytosis risk, because the outcome definition included neutropenia in addition to agranulocytosis and the proportion of patients with malignancies and chemotherapy was higher than in the control group [7]. In the Berlin Case-Control Surveillance Study, approximately 2 million defined daily doses (DDD) of metamizole were dispensed per metamizole-induced agranulocytosis case, corresponding to ~143,000 two-week courses at standard dosing or 0.96 cases per million population per year [8].

ABBREVIATIONS / GLOSSARY OF TERMS

4-MAA 4-methylaminoantipyrine (also: N-methyl-4-aminoantipyrine); primary active metabolite of metamizole
ADR Adverse drug reaction
ATC Anatomical Therapeutic Chemical classification system
BOXED WARNING Strongest warning in product information to highlight a serious risk
CI Confidence interval
DDD Defined daily dose; the DDD is the assumed average maintenance dose per day for a drug's main adult indication
DHPC Direct Healthcare Professional Communication; safety notice to healthcare professionals on important safety information
EMA European Medicines Agency
FBC Full blood count
HLA Human leucocyte antigen
ICSR Individual case safety report
LVEF Left ventricular ejection fraction
MAH Marketing authorisation holder
MEDDRA Medical Dictionary for Regulatory Activities
NSAID Non-steroidal anti-inflammatory drug
PRAC Pharmacovigilance Risk Assessment Committee (EMA)
SMQ Standardised MedDRA Query
UMC Uppsala Monitoring Centre (WHO Programme for International Drug Monitoring)
VIGIBASE WHO global database of individual case safety reports (ICSR), maintained by the UMC
VIGILYZE Web-based analytics and signal-detection interface to VigiBase (UMC)
WHO World Health Organization

The pathophysiology of metamizole-induced agranulocytosis remains controversial; immune-mediated mechanisms and direct toxic/metabolic effects have been discussed [6, 9]. To date, no robust HLA association or genome-wide risk locus has been identified for metamizole-induced agranulocytosis [10, 11]. Reported case-fatality rates range from 5% to 23.6% [6], but early treatment with granulocyte colony-stimulating factor (e.g. filgrastim) can shorten the duration of neutropenia and is associated with improved clinical outcomes [12].

In a German retrospective analysis (1990–2012), ≥25% of metamizole-induced agranulocytosis cases were associated with off-label use: ~70% for mild-to-moderate pain and ~30% for first-line fever. Only 3.1% occurred within the licensed indication (high-grade fever unresponsive to other therapy), where recognition is particularly difficult because of symptom overlap [13]. A recent report confirmed a continued increase in off-label metamizole use [14].

This article describes metamizole utilisation in Switzerland, summarises post-marketing safety reporting on metamizole-induced agranulocytosis and outlines the rationale and scope of recently implemented regulatory measures. We additionally examined fatal metamizole-induced agranulocytosis individual case safety reports (ICSR) in VigiLyze to characterise frequently co-reported concomitant medicines and to screen for potential drug-drug interaction signals (e.g. methotrexate).

Methods

Data sources

Utilisation

Exposure was defined as total DDD per calendar year across outpatient and inpatient distribution channels and all formulations. Aggregated national sales data were obtained from all marketing authorisation holders (MAH) of metamizole-containing medicinal products marketed in Switzerland, covering all dosage forms (tablets, drops, ampoules, suppositories) and the period 2014–2023. These data were provided as part of a regulatory procedure to characterise exposure and time trends. Sales data were converted to DDD using the WHO ATC/DDD assignment for metamizole (N02BB02; 3 g/day across oral, parenteral and rectal routes) [15]. Sales-based DDDs are a supply-based proxy and may be influenced by inventory dynamics (stocking, returns, wastage). Results are presented as market-level aggregates across MAHs.

Spontaneous reporting data

Swissmedic collects and assesses ICSRs and transmits them to the Uppsala Monitoring Centre (UMC) for inclusion in VigiBase, the World Health Organization's (WHO) global database of spontaneous safety reports. Data were retrieved from VigiBase via VigiLyze, the UMC web-based analysis interface. The primary analysis used Swiss ICSRs; global data were extracted for contextual comparisons. All extractions used the 27 August 2025 VigiLyze data snapshot.

Case identification

Searches captured metamizole/dipyrone at ATC N02BB (class level) and required the drug to be recorded as suspect or interacting. Reactions were identified using the MedDRA SMQ "Agranulocytosis" (narrow) (MedDRA v28.0).

Outcome and deduplication

Fatal outcome status was taken as coded in VigiLyze. Potential duplicates were handled using UMC's automated deduplication, supplemented by targeted manual review of remaining potential duplicates.

Interpretation caveats

As with all spontaneous reporting systems, the data are subject to underreporting, variable report quality and missing information, and do not provide incidence estimates. Cross-country comparisons may be influenced by differences in exposure, reporting practices and case ascertainment.

Methotrexate co-reporting

Co-reporting was assessed in VigiLyze by reviewing the medication list of fatal Swiss metamizole-induced agranulocytosis ICSRs and flagging cases in which methotrexate was recorded as a concomitant drug (based on the ICSR drug-role field). For this analysis, we used the full Swiss fatal metamizole-induced agranulocytosis set irrespective of onset year (initial report dates 2011–2025; VigiLyze snapshot 27 August 2025) and compared it with the corresponding global fatal set.

Indicators and statistical analysis

Annual counts of Swiss spontaneous reports of metamizole-induced agranulocytosis and annual metamizole utilisation were summarised by calendar year. Utilisation was expressed in DDD. The utilisation-normalised reporting rate was calculated for each year as the number of metamizole-induced agranulocytosis reports divided by annual utilisation and expressed as reports per million DDD.

Time trends in utilisation-normalised reporting rates were assessed using ordinary least-squares linear regression with calendar year as the predictor and the annual utilisation-normalised reporting rate as the outcome (absolute change per year). For the regression slope, we report the point estimate and 95% confidence intervals (CI) derived from the slope estimate and its standard error using the t-distribution. Analyses were performed in Microsoft Excel 2024 (Microsoft Corporation, Redmond, WA, USA). Given the small number of annual observations, model fit and assumptions were assessed by visual inspection of the fitted trend and residual diagnostic plots; results should be interpreted descriptively.

Ethics approval was not required.

Open science

Protocol and registration

This work was conducted as part of a pharmacovigilance safety signal assessment to support regulatory risk-minimisation activities. No a priori study protocol was prepared, and the work was not registered in a public registry; protocol deviations are therefore not applicable.

Code

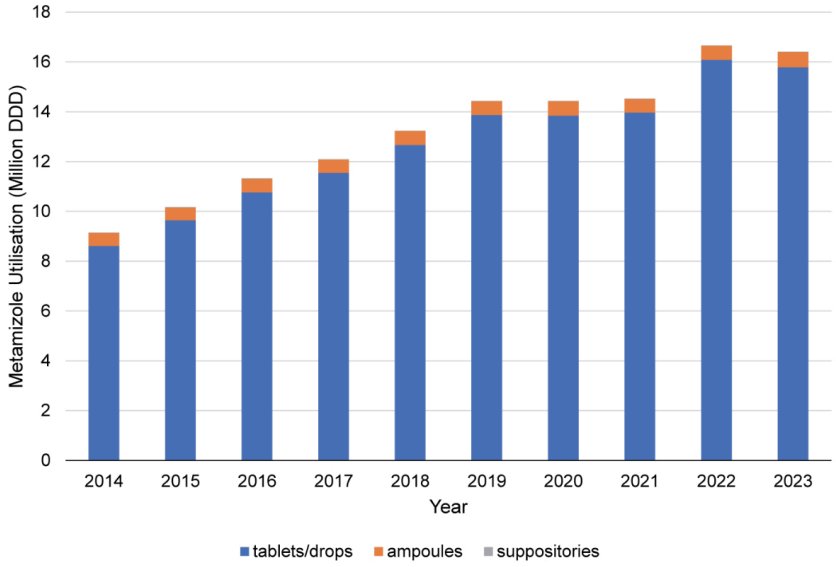
All analyses were performed in Microsoft Excel 2024. No additional software libraries, frameworks or packages were used, and no standalone analytical scripts were developed; therefore, there is no analytical code to share.

Results

Metamizole utilisation in Switzerland (2014–2023)

Metamizole utilisation in Switzerland rose markedly over the past decade. Based on aggregated sales data, total DDD (see Methods) increased from 9,154,329 in 2014 to 16,410,403 in 2023 – an overall rise of ~79% (figure 1). Across 2014–2023, the cumulative formulation mix was 95.7% tablets/drops, 4.2% ampoules and 0.1% suppositories.

Figure 1: Annual metamizole utilisation in Switzerland (2014–2023). Annual metamizole DDD estimated from aggregated national sales data (outpatient and inpatient), stratified by formulation (see Methods). The contribution from suppositories is too small to be visible at this y-axis scale.



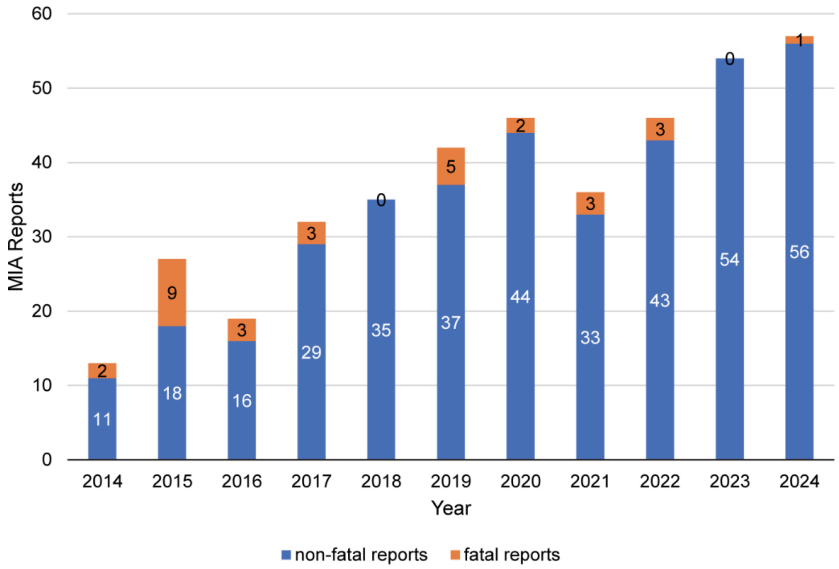
Pharmacovigilance findings on metamizole-induced agranulocytosis (2014–2024)

Spontaneous ICSRs were retrieved from VigiBase (see Methods).

We identified 407 Swiss ICSRs of metamizole-induced agranulocytosis for 2014–2024, of which 31 (7.6%) were classified as fatal. For the methotrexate co-reporting analysis, we used a broader fatal set (2011–2025; n = 38); proportions are therefore calculated on 38.

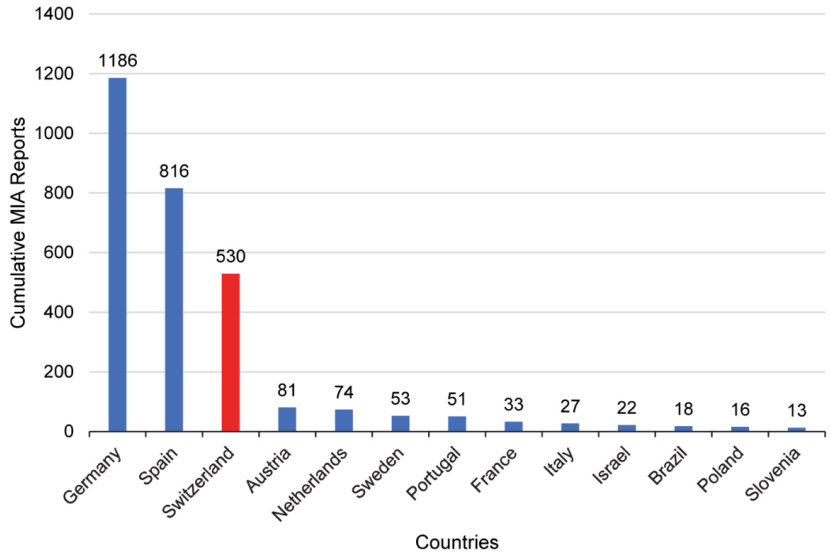
Annual report counts increased from 13 (2014) to 57 (2024) with marked variability (median 36; range 13–57). The fatal fraction declined across periods: 13.5% (17/126) in 2014–2018, 5.8% (13/224) in 2019–2023 and 1.8% (1/57) in 2024 (figure 2). Case summaries showed no consistent age predominance. Co-reported methotrexate was noted in 39.5% (15/38) of Swiss fatal metamizole-induced agranulocytosis ICSRs in the full Swiss fatal set (initial dates 2011–2025) versus 19.8% (48/243) globally, suggesting a potential interaction signal but subject to confounding and reporting biases.

Figure 2: Annual spontaneous reports of metamizole-induced agranulocytosis in Switzerland, 2014–2024. Source: VigiLyze (see Methods).



Internationally, Switzerland contributes a disproportionately high absolute number of cumulative metamizole-induced agranulocytosis reports compared with many larger countries (figure 3). Cross-country comparisons should be interpreted cautiously because exposure denominators and reporting practices differ.

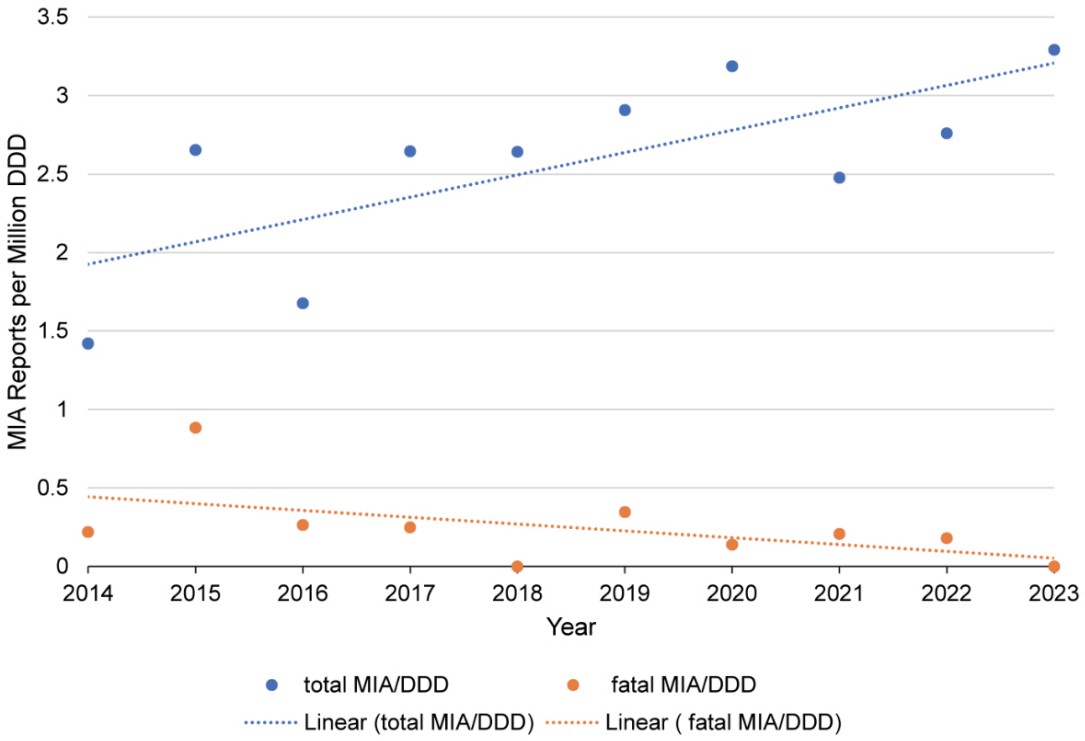
Figure 3: Cumulative global metamizole-induced agranulocytosis reports by country. Switzerland is highlighted in red. Source: VigiLyze (see Methods).



The utilisation-normalised reporting rate increased from 1.42 to 3.29 reports of metamizole-induced agranulocytosis per million DDD. Aggregated by period, rates were 2.25 per million DDD in 2014–2018 vs 2.93 in 2019–2023 (rate ratio 1.30). Fatal reporting rates remained low and trended downward (0.304 vs 0.170 per million DDD; rate ratio 0.56). Across 2014–2023, mean rates were 2.566 (total) and 0.249 (fatal) reports per million DDD.

When fitted by linear regression, the utilisation-normalised reporting rate of metamizole-induced agranulocytosis increased by 0.142 reports per million DDD per year (95% CI 0.031 to 0.253), whereas the fatal utilisation-normalised reporting rate showed a weak downward trend (-0.043 reports per million DDD per year; 95% CI -0.100 to 0.013), with no fatal reports in 2023 (figure 4).

Figure 4: Annual Swiss utilisation-normalised reporting of metamizole-induced agranulocytosis (reports per million DDD), 2014–2023, with fitted linear trend lines. Denominator: total DDD from aggregated national sales (outpatient and inpatient). Reports: VigiLyze. Utilisation data were available to 2023 only (see Methods).



Regulatory actions

In response to rising metamizole exposure and persistent reports of metamizole-induced agranulocytosis in Switzerland, Swissmedic conducted a reassessment and introduced additional measures to mitigate metamizole-induced agranulocytosis risk, including:

- targeted education to improve early recognition of metamizole-induced agranulocytosis by healthcare professionals and patients;
- reduction of off-label use, which is considered a contributing factor to increased exposure [13, 14]; and
- avoidance of concomitant use with methotrexate due to an increased risk of haematotoxicity.

In parallel, the EMA initiated a referral procedure for metamizole (Article 107i) [16]. Several recommendations of the Pharmacovigilance Risk Assessment Committee (PRAC) have already been incorporated into the Swiss prescribing information, notably:

- contraindications for patients with a history of metamizole-induced agranulocytosis, bone-marrow dysfunction or haematological disorders; and
- clarified information on duration of use (while routine blood count monitoring had not been recommended previously).

The Swiss product information was further updated to include a boxed warning emphasising the risk of agranulocytosis and the importance of early symptom recognition, with specific guidance on the interaction between metamizole and methotrexate; co-administration should be avoided. This includes the instruction to discontinue metamizole and perform an immediate blood count if agranulocytosis is suspected, and to stop treatment pending results [17]. Indications were revised to reinforce appropriate use:

– **Pain:** use only for severe pain when other non-opioid analgesics are ineffective or contraindicated, confirming a second-line role.
– **Fever:** use only for high fever that does not respond to other medicinal treatments.

To enhance patient awareness, a red-framed statement was added to the outer packaging instructing patients to consult the leaflet before use.

A Direct Healthcare Professional Communication (DHPC) informed Swiss healthcare providers of these changes. A side-by-side summary of measures adopted by Swissmedic versus PRAC recommendations is provided in table 1.

Table 1: Comparative summary of risk-minimisation measures and safety communications (EMA vs Swissmedic).

Domain	Measure	Content	EMA	Swissmedic
Product information	Boxed warning	On metamizole-induced agranulocytosis	✓	✓
		Avoid concomitant use with methotrexate	×	✓
	Therapeutic indications	More precise definition / restriction	×	✓
	Contraindications	Clarified (history of metamizole-induced agranulocytosis, bone-marrow dysfunction, haematological disease)	✓	✓
	Warnings / Precautions	Strengthened information on agranulocytosis (early recognition, immediate FBC, stop treatment pending results)	✓	✓
		Interaction with methotrexate	×	✓
Outer carton (secondary packaging)	Red-framed warning on outer carton	Directing patients to read the package leaflet	×	✓
Safety communication	DHPC		✓ *	✓ [17]

DHPC: Direct Healthcare Professional Communication.
* National implementation example (Germany): Federal Institute for Drugs and Medical Devices (BfArM) [18]

Discussion

Between 2014 and 2023, metamizole utilisation in Switzerland increased markedly. Over the same period, both the absolute number of Swiss spontaneous metamizole-induced agranulocytosis reports and the utilisation-normalised reporting rate increased. Reporting activity thus expanded faster than utilisation, which may be compatible with intensified pharmacovigilance awareness and case-finding, and possibly with shifts in use patterns (e.g. more methotrexate co-medication).

In contrast, utilisation-normalised fatal reporting decreased over time and was very low towards the end of the observation period. The fatal proportion likewise declined. These patterns may be compatible with earlier recognition and improved management, and/or shifts in case mix; however, random variability, residual confounding and reporting biases cannot be excluded. Notably, methotrexate was more frequently co-reported in Swiss fatal cases than in the global fatal set, which may indicate a potential interaction signal, though confounding by indication (e.g. underlying malignancy, tumour pain) remains a plausible alternative explanation.

Switzerland's comparatively large share of global metamizole-induced agranulocytosis reports may reflect robust national pharmacovigilance practices and infrastructure, rather than necessarily higher intrinsic risk. Spontaneous adverse drug reactions (ADR) are known to be substantially under-reported, including in general practice, which may contribute to differences in reporting completeness across settings [19]. Severe cases such as agranulocytosis often require hospital evaluation, which may increase the likelihood of recognition, laboratory confirmation and subsequent reporting. Computerised monitoring approaches using laboratory triggers and electronic health data have been described as tools that can support detection and reporting of ADRs [20]. Consistent with this, approximately 80% of Swiss national ICSRs originate from regional pharmacovigilance centres based at university hospitals (internal Swissmedic estimate), which may contribute to more complete documentation of serious ADRs such as agranulocytosis. Practically, the data are aligned with risk-minimisation priorities: restrict use to licensed/approved indications, coun-

sel patients on early warning symptoms (with immediate discontinuation and urgent blood count at first signs) and avoid concomitant methotrexate; these measures are intended to maintain benefit while minimising preventable harm.

Regulatory assessments by EMA and Swissmedic concluded that, despite the established risk of agranulocytosis, the benefit–risk profile remains favourable when metamizole is used appropriately and action is taken promptly at first symptoms. Within the analgesic landscape, especially in patients at heightened risk from NSAIDs or opioids, in older adults or where alternative non-opioid analgesics are ineffective or unsuitable, metamizole remains an option with appropriate safeguards. The effectiveness of implemented measures should be evaluated using complementary indicators: pharmacovigilance trends (including severity), prescribing/exposure analyses, awareness/process metrics and clinical outcomes (hospitalisation, mortality). Risk-minimisation measures cannot eradicate an idiosyncratic event such as agranulocytosis; rather, they aim to reduce exposure outside approved indications and to avert severe outcomes through patient counselling, early detection and prompt clinical response.

If current measures prove insufficient, targeted regulatory or educational actions could be considered (e.g. tighter control of dispensing channels, prescriber education/certification or stricter initiation criteria). As one model, the Netherlands restricts oral metamizole to short-term use (≤14 days), initiated by a hospital-based pain specialist and dispensed via hospital/outpatient pharmacies [21, 22].

Finally, linking sales-based DDD to spontaneous reports is valuable for tracking signal evolution but does not establish incidence or risk. DDD aggregates reflect volumes dispensed, not person-time or treatment courses; spontaneous reports are subject to under- and differential reporting and incomplete clinical detail. Accordingly, utilisation-normalised reporting should be interpreted primarily as an indicator of pharmacovigilance activity, not a direct population risk estimate.

Conclusion

Metamizole utilisation increased alongside higher numbers of reported metamizole-induced agranulocytosis cases, while fatal outcomes in spontaneous reports declined. These findings describe reporting patterns but do not allow conclusions about true incidence or the effectiveness of risk minimisation measures. The data are consistent with continued access to metamizole alongside targeted risk-minimisation, ongoing patient counselling and continued pharmacovigilance, and event-triggered benefit–risk re-evaluation to sustain benefit while minimising preventable harm.

Data sharing statement

Deidentified, aggregated data supporting the findings (annual utilisation in DDD, annual Swiss metamizole-induced agranulocytosis report counts, utilisation-normalised reporting rates and a data dictionary) will be made available from the corresponding author upon reasonable request. Individual case-level spontaneous report data and company-level sales data are not publicly shareable due to database access restrictions and confidentiality obligations. Requests will be assessed for scientific purpose, feasibility and compliance with applicable permissions.

Acknowledgments

Spontaneous reporting data were accessed via VigiLyze. Data providers had no role in the study design, analysis, interpretation, manuscript preparation or the decision to submit. The views expressed are those of the authors and do not necessarily represent the positions of WHO, UMC or Swissmedic.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed. Aggregated sales/exposure data were provided by MAHs in the context of a pharmacovigilance safety signal evaluation; the MAHs had no role in study design, analysis, interpretation, manuscript preparation or the decision to submit.

References

1. Fendrich Z . [Metamizol—a new effective analgesic with a long history. Overview of its pharmacology and clinical use]. Cas Lek Cesk. 2000 Jul;(14):440–4.PMID: 11048407 ISSN: 0008-7335
2. Bachmann F , Meyer Zu Schwabedissen HE , Duthaler U , Krähenbühl S . Cytochrome P450 1A2 is the most important enzyme for hepatic metabolism of the metamizole metabolite 4-methylaminoantipyrine. Br J Clin Pharmacol. 2022 Feb;(4):1885–96. https://doi.org/10.1111/bcp.15108 PMID: 34648192 ISSN: 1365-2125
3. Bachmann F , Duthaler U , Meyer Zu Schwabedissen HE , Puchkov M , Huwyler J , Haschke M , et al. Metamizole is a Moderate Cytochrome P450 Inducer Via the Constitutive Androstane Receptor and a Weak Inhibitor of CYP1A2. Clin Pharmacol Ther. 2021 Jun;(6):1505–16. https://doi.org/10.1002/cpt.2141 PMID: 33336382 ISSN: 1532-6535
4. Lutz M . Metamizole (Dipyrone) and the Liver: A Review of the Literature. J Clin Pharmacol. 2019 Nov;(11):1433–42. https://doi.org/10.1002/jcph.1512 PMID: 31433499 ISSN: 1552-4604
5. Gut S , Rauch M , Haschke M , Huber CA , Gaertner J , Schur N , et al. Use of metamizole and other non-opioid analgesics in Switzerland between 2014 and 2019: an observational study using a large health insurance claims database. Swiss Med Wkly. 2024;154(3535. https://doi.org/https://doi.org/10.57187/s.3535.
6. Tomidis Chatzimanouil MK , Goppelt I , Zeissig Y , Sachs UJ , Laass MW . Metamizole-induced agranulocytosis (MIA): a mini review. Mol Cell Pediatr. 2023 Aug;(1):6. https://doi.org/10.1186/s40348-023-00160-8 PMID: 37589909 ISSN: 2194-7791
7. Klose S , Pflock R , König IR , Linder R , Schwaninger M . Metamizole and the risk of drug-induced agranulocytosis and neutropenia in statutory health insurance data. Naunyn Schmiedebergs Arch Pharmacol. 2020 Apr;(4):681–90. https://doi.org/10.1007/s00210-019-01774-4 PMID: 31811328 ISSN: 1432-1912
8. Huber M , Andersohn F , Sarganas G , Bronder E , Klimpel A , Thomae M , et al. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin Case-Control Surveillance Study. Eur J Clin Pharmacol. 2015 Feb;(2):219–27. https://doi.org/10.1007/s00228-014-1777-8 PMID: 25378038 ISSN: 1432-1041
9. Rudin D , Roos NJ , Duthaler U , Krahenbuhl S . Toxicity of metamizole on differentiating HL60 cells and human neutrophil granulocytes. Toxicology. 2019;426(152254. https://doi.org/https://doi.org/10.1016/j.tox.2019.152254.
10. Cismaru AL , Rudin D , Ibañez L , Liakoni E , Bonadies N , Kreutz R , et al. Genome-Wide Association Study of Metamizole-Induced Agranulocytosis in European Populations. Genes (Basel). 2020 Oct;(11):1275. https://doi.org/10.3390/genes11111275 PMID: 33138277 ISSN: 2073-4425
11. Cismaru AL , Grimm L , Rudin D , Ibanez L , Liakoni E , Bonadies N , et al. High-Throughput Sequencing to Investigate Associations Between HLA Genes and Metamizole-Induced Agranulocytosis. Front Genet. 2020;11(951. https://doi.org/https://doi.org/10.3389/fgene.2020.00951.
12. Andrès E , Maloisel F , Zimmer J . The role of haematopoietic growth factors granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor in the management of drug-induced agranulocytosis. Br J Haematol. 2010 Jul;(1):3–8. https://doi.org/10.1111/j.1365-2141.2010.08104.x PMID: 20151980 ISSN: 1365-2141
13. Stammschulte T , Ludwig WD , Mühlbauer B , Bronder E , Gundert-Remy U . Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990-2012. Eur J Clin Pharmacol. 2015 Sep;(9):1129–38. https://doi.org/10.1007/s00228-015-1895-y PMID: 26169297 ISSN: 1432-1041
14. Lübow C , Rotthauwe J , Behles C. Metamizol: schwerwiegende Nebenwirkungen – Update. Bulletin zur Arzneimittelsicherheit. 2022;4):24-8.
15. WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD Index . 2025 [Available from: https://atcddd.fhi.no/atc_ddd_index/?code=N02BB02
16. Measures to minimise serious outcomes of known side effect with painkiller metamizole (EMA/407900/2024) [updated 6 December 2024. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/metamizole-containing-medicinal-products-0
17. DHPC – Novalgin . Metamizol Spirig HC, Minalgin, Novaminsulfon Sintetica, Metamizol-Mepha (metamizolum) 2025 [Available from: https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/health-professional-communication--hpc-/dhpc-metamizolum.html
18. Rote-Hand-Brief zu metamizolhaltigen Arzneimitteln: Wichtige Maßnahmen zur Minimierung der schwerwiegenden Folgen des bekannten Risikos für Agranulozytose 2024 [Available from: https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2024/rhb-metamizol.html?nn=591002
19. Hazell L , Shakir SA . Under-reporting of adverse drug reactions : a systematic review. Drug Saf. 2006;(5):385–96. https://doi.org/10.2165/00002018-200629050-00003 PMID: 16689555 ISSN: 0114-5916
20. Molokhia M , Tanna S , Bell D . Improving reporting of adverse drug reactions: Systematic review. Clin Epidemiol. 2009;1(75-92. https://doi.org/https://doi.org/10.2147/clep.s4775. https://doi.org/10.2147/CLEP.S4775
21. Metamizol 2024 [Available from: https://richtlijnendatabase.nl/richtlijn/postoperatieve_pijn/kinderen_-_postoperatieve_pijn/medicamenteuze_interventies_kinderen/metamizol_-_postoperatieve_pijn_kinderen.html
22. Public Assessment Report - Dolamizol 250 mg and 500 mg tablets (metamizole sodium monohydrate): Medicines Evaluation Board (MEB) of the Netherlands; 2021 [Available from: https://www.geneesmiddeleninformatiebank.nl/pars/h124159.pdf