International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 24-03-2024, Accepted: 14-04-2024, Published: 08-05-2024
Volume 9, Issue 2, 2024, Page No. 4-7

Diroximel fumarate: An overview

Mohammad Atika Afreen Shafi[2], Gangu Sreelatha[1*], K Ratna Jyothi[2], Tadikonda Rama Rao[2]
[1] Assistant Professor, Department of Pharmaceutical Analysis, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India
[2] Department of Pharmaceutical Analysis, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, Telangana, India

Abstract
Diroximel fumarate, sold under the brand name Vumerity, is a medication used for the treatment of relapsing forms of multiple sclerosis (MS). It acts as an immunosuppressant and anti-inflammatory drug. Diroximel fumarate is hypothesized to regulate cell signalling pathways, causing beneficial immune and neuroprotective effects. It is prescribed for the treatment of relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults. Its most common adverse effects are flushing and gastrointestinal problems. The drug is available as a white delayed-release capsule that is resistant to gastric acid and only dissolves in the intestine. Under the European Union's label, the drug is contraindicated in people with progressive multifocal leukoencephalopathy (PML), a disease of the brain caused by a virus. In the US, combination with the closely related drug dimethyl fumarate is contraindicated.

Keywords: Vumerity, multiple sclerosis, immunosuppressant, cell signalling

Introduction

Relapsing forms of Multiple Sclerosis (MS) are treated with a medication called Diroximel fumarate [1]. MS is a chronic immune-mediated central nervous system (CNS) disorder whose first clinical episode usually manifests in a person between the ages of 20 and 30 [2].

A neurological disease that can cause severe physical and cognitive symptoms, multiple sclerosis (MS) is a chronic and debilitating condition that may significantly decrease quality of life. It is the primary cause of neurological impairment in young adults that is not brought on by trauma. Neurological symptoms in relapsing-remitting MS patients resolve and recur on a regular basis. Over 80% of individuals afflicted with this illness have relapsing-remitting multiple sclerosis.

A newly discovered medication in the fumarate class, Diroximel fumarate is intended to treat multiple relapsing forms of multiple sclerosis. This medication is bioequivalent to dimethyl fumarate, but because of its distinct chemical makeup, it is less likely to have adverse effects in the gastrointestinal tract. Alkermes worked with Biogen to formulate Diroximel fumarate, which received FDA approval in October 2019 and EMA approval in November 2021 [1].

Introduction

A class of drugs known as Nrf2 activators includes Diroximel fumarate. It functions by reducing inflammation and shielding nerve damage from developing, which could lead to multiple sclerosis symptoms [3]. Relapsing remitting multiple sclerosis (rrms), clinically isolated syndrome (cis), and active secondary progressive multiple sclerosis (ASPS) are the conditions for which Diroximel fumarate, also known by its generic name, Diroximel fumarate, is prescribed. It is marketed under the brand name Vumerity. It has anti-inflammatory and immunosuppressive properties. Flushing and gastrointestinal issues are the most frequent side effects [4].

A white delayed-release capsule containing Diroximel fumarate is available; it dissolves only in the intestine and is resistant to gastric acid [4]. This release of the medication occurs in the intestine to avoid disruption by stomach acids. Diroximel fumarate is a treatment option for adults suffering from various forms of multiple sclerosis (MS), a disease characterized by nerve failure resulting in weakness, numbness, loss of muscle coordination, and difficulties with vision, speech, and bladder control. These forms include: (i) clinically isolated syndrome (CIS; nerve symptom episodes lasting at least 24 hours), (ii) relapsing-remitting forms (a disease course in which symptoms flare up occasionally), or (iii) secondary progressive forms (a disease course where relapses occur more frequently) [3]. Formula for chemicals is C_{11} H_{13} NO_6.

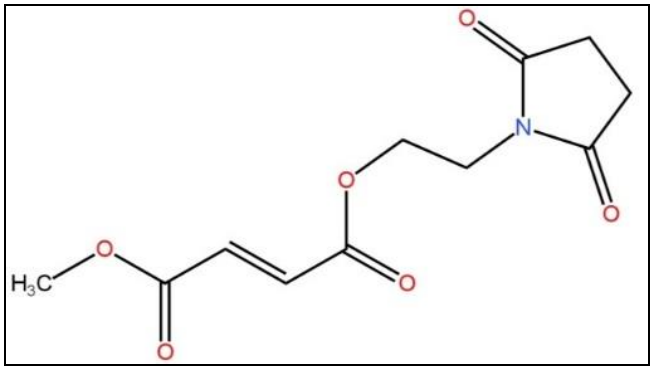

Fig 1: Structure of Diroximel fumarate

Mechanism of action

There is currently a lack of complete understanding regarding the drug's mechanism of action in MS [1]. Preclinical research revealed that it triggered the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2), which is upregulated in response to oxidative stress [4]. The anti-inflammatory and neuroprotective effects of Diroximel fumarate are thought to be caused by

modulating cell signalling pathways [5]. When Diroximel fumarate is metabolized, the active form produced is monomethyl fumarate (MMF), which in humans stimulates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2). When cells experience oxidative stress, this pathway gets activated.

In addition, MMF functions as an agonist of the nicotinic acid receptor in a lab setting. As of yet, it is unknown how important this finding is for treating multiple sclerosis. The absence of a methanol leaving group in its chemical structure and replacement with inert 2-hydroxyethyl succinimide are thought to be the mechanisms by which this medication has fewer gastrointestinal side effects [1, 6].

Pharmacokinetics

The principal inactive metabolite is hydroxyethyl succinimide (HES), while the active metabolite is monomethyl fumarate (MMF). It has been discovered that Diroximel fumarate and dimethyl fumarate have nearly the same pharmacokinetics. Both of these are monomethyl fumarate prodrugs. While taking the medication with a high-calorie, high-fat meal slows down absorption, it has no discernible impact on absorption overall. It is advised by the US label not to take the medication with meals that are heavy in fat and calories. It is broken down by esterase enzymes after consumption so that the inactive metabolite hydroxyethyl succinimide (HES) and the active metabolite monomethyl fumarate (MMF) can be released into the bloodstream later on. The blood does not contain Diroximel fumarate per se. 2.5 to 3 hours after consumption, MMF concentrations in blood plasma are at their maximum. Between 27 and 45 percent are bound to plasma proteins while in circulation. After being further broken down into fumarate, citrate, and glucose, MMF eventually enters the citric acid cycle and is converted to carbon dioxide (CO2). Approximately 60% of the material is expelled from the body through the lungs as CO2, 15.5% is eliminated through urine (less than 0.3%, per another source), and 0.9% is eliminated through feces. An hour is the terminal half-life. Urine is the primary means of HES elimination (58–63%) [4, 7].

Pharmacodynamics

Compared to dimethyl fumarate, which is its bioequivalent, Diroximel fumarate has less gastrointestinal side effects and relieves the neurological symptoms of relapsing multiple sclerosis. Remember that Diroximel fumarate can result in flushing, lymphopenia, angioedema, anaphylaxis, hepatotoxicity, and Progressive Multifocal Leukoencephalopathy (PML) [1, 8].

If anaphylaxis or edema develops, stop taking Diroximel fumarate right away if PML is suspected. Before starting Diroximel fumarate and throughout treatment, liver function and total bilirubin should be evaluated. Before initiating the use of Diroximel fumarate, as well as after the first six months of treatment, a complete blood count (CBC) should be taken. This should also be done every six to twelve months subsequently. After more than six months, stop treatment if lymphocyte counts are less than 0.5 × 109/L.

Absorption

Similar to its bioequivalent medication, dimethyl fumarate, Diroximel fumarate is quickly absorbed in the digestive system after being administered. After oral administration, monomethyl fumarate's (MMF) median T_{max} varies from 2.5 to 3 hours, while its mean C_{max} is 2.11 mg/L. When given to healthy participants, the bioequivalent medication dimethyl fumarate likewise exhibits a comparable mean T_{max} and C_{max}.

After this metabolite is given twice daily to MS patients, the average steady state concentration is estimated to be 8.32 mg.hr/L. 88 mg × min L−1 is the active metabolite's mean AUC0–∞. When compared to administration during fasting, food appears to significantly lower the C_{max} of MMF, the active metabolite of Diroximel fumarate [1, 9].

Volume of distribution

The distribution's apparent volume falls between 72 and 83L. The active metabolite of Diroximel fumarate that penetrates the blood brain barrier is monomethyl fumarate (MMF).

Protein binding

The range of plasma protein binding for MMF, which is the active metabolite of Diroximel fumarate, is 27–45%.

Metabolism

Both Diroximel fumarate and its bioequivalent medication, dimethyl fumarate, are extensively metabolized in the liver by esterases. The gastrointestinal system, tissues, and blood all contain large concentrations of these enzymes. Prior to entering the bloodstream, this medication undergoes esterase metabolism, which yields monomethyl fumarate (MMF), the active metabolite. Along with trace amounts of methanol and another inactive metabolite, RDC-8439, the main inactive metabolite, 2-hydroxyethyl succinimide (HES), is also produced. MMF is further metabolized by the tricarboxylic acid (TCA) cycle after esterase metabolism. Fumaric acid, citric acid, and glucose are the three main MMF metabolites found in plasma. Due to its lower risk of gastrointestinal side effects, it is significant that methanol is a minor metabolite of Diroximel fumarate metabolism but a major metabolite of dimethyl fumarate metabolism [1, 10].

Route of elimination

Carbon dioxide from exhaled breath is used to remove monomethyl fumarate. Less than 0.3% of the administered dose, or negligible amounts, are determined in urine. Urine contains 2-hydroxyethyl succinimide (HES), an inactive metabolite that accounts for 58–66% of the dose that was consumed.

Half-Life

Monomethyl fumarate (MMF) is the active metabolite of Diroximel fumarate. Its terminal half-life is estimated to be one hour.

Clearance

Diroximel fumarate does not currently have an MSDS available. An oral LD50 of 2,240 mg/kg in rats is indicated by the MSDS for dimethyl fumarate, its bioequivalent counterpart. The FDA label for Diroximel fumarate contains no information regarding overdose. There have been documented overdose cases with dimethyl fumarate, its bioequivalent counterpart, in the literature, and the symptoms are indicative of the negative effects of this medication. In addition to other symptoms, these include flushing, nausea, vomiting, and diarrhoea. The overdose of

diroximel or dimethyl fumarate currently has no known counteragent. So far, the only options available in the event of an overdose are supportive and symptomatic management [1, 14].

Contraindications

According to the European Union label, the medication should not be administered to patients who have progressive multifocal leukoencephalopathy (PML), a virus-related brain disease. Combining this medication with the closely related dimethyl fumarate is not advised in the United States [4, 11].

Side Effects

There are no comprehensive studies on the side effects of Diroximel fumarate available. Flushing (in 34% of patients treated with the drug, versus 5% in the placebo group) and gastrointestinal side effects, including diarrhoea (14% versus 10%), nausea (12% versus 9%), abdominal pain (9% versus 4%), vomiting (8% versus 5%), and indigestion (5% versus 3%), were the most common side effects in dimethyl fumarate studies. Four percent of patients discontinued the treatment due to gastrointestinal side effects, and three percent did so due to flushing. PML, which has been reported while receiving dimethyl fumarate, is an uncommon but potentially deadly side effect [4].

There may be adverse effects from Diroximel fumarate. If any of the following symptoms are severe or persistent, let your doctor know: stomach pain, diarrhoea, nausea, vomiting, heartburn, warmth, redness, itching, or burning of the skin; hair loss.

Some side effects, which can be quite serious, include: trouble breathing or swallowing, hives, rash, swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs, clumsiness in your arms or legs, vision problems, changes in thinking and memory, confusion, changes in personality, fatigue, appetite loss, stomach pain on the right side, dark urine, yellowing of the skin or eyes, burning, tingling, itching, or skin sensitivity on one side of the body or face, followed by a painful rash or blisters that appear several days later.

Interactions

The cytochrome P450 enzymes and P-glycoprotein are not impacted by Diroximel fumarate. Between 27 and 45 percent of plasma proteins bind to monomethyl fumarate, its active metabolite. Thus, it is thought to have little chance of causing pharmacokinetic interactions. Based on experience with other immunosuppressive medications, such as studies with tetanus, pneumococcal, and meningococcal vaccines, inactivated vaccines may be administered underDiroximel fumarate therapy. There have been no studies done on the efficacy of these vaccinations when Diroximel fumarate is present. There are no data on the use of immunosuppressants, chemotherapy, or live vaccines together. Combining themedication with diuretics, NSAIDs, aminoglycoside antibiotics, or lithium may increase nephrotoxicity [4, 15].

Drug Interaction

Alefacept, Adalimumab, Aldesleukin, and Abatacept, among others: Combining a medication with Diroximel fumarate may increase the likelihood or intensity of side effects. Live vaccine for adenovirus type 7Combining the live Adenovirus type 7 vaccine with Diroximel fumarate may increase the risk or severity of infection.

Food Interactions

Stay away from alcohol, Consume with or without food. A meal or snack should not exceed 700 calories and not more than 30 grams of fat if consumed with food. Diroximel fumarate may lessen the side effects of flushing when taken with food [1, 17].

Chemical taxonomy

- Description: This particular compound is a member of the fatty acid esters class of organic compounds. They are fatty acid derivatives with carboxylic ester functionality.
- IUPAC name: 4-O-[2-(2,5-dioxopyrrolidin-1-yl) ethyl] 1-O-methyl (E)-but-2-enedioate
- Class: Fatty Acyls
- Super Class: Lipids and lipid-like molecules
- Sub Class: Fatty acid esters
- Kingdom: Organic compounds
- Direct Parent: Fatty acid esters
- Substituents:2-pyrrolidone, alpha, beta-unsaturated carboxylic ester, azacycle, carbonyl group, carboxylic acid derivative, carboxylic acid ester, carboxylic acid imide, n-substituted, and dicarboximide are examples of heterocyclic compounds.
- Alternative Parents: N-substituted carboxylic acid imides, N-alkyl pyrrolidines, dicarboxylic acids and their derivatives, and pyrrolidine-2-ones Organonitrogen compounds, lactams, methyl esters, enoate esters, dicarboximides, and azacyclic compounds.
- Molecular Framework: Aliphatic heteromonocyclic compounds
- Affected organisms: Humans.

Properties

Table 1: Properties of Diroximel fumarate

Characteristic	Diroximel fumarate
State	Solid
Melting Point	102^0C-106^0C
Boiling Point	192^0C-193^0C
Log P	0.74

Storage of the Drug

- Medication is securely closed in its container and kept out of children's reach. Keep it away from extreme heat and moisture, and store at room temperature.
- As many medication containers (such as weekly pill minders and those for eye drops, creams, patches, and inhalers) are not child-resistant and young children can easily open them, it is crucial to keep all medication out of sight and reach of children. Always lock safety caps on medications to prevent poisoning in small children. It is important to dispose unnecessary medications in a specific manner so that children, pets, and other people cannot ingest them [19].

Particular safety measures need to be taken before consuming Diroximel fumarate

- One should be aware that Diroximel fumarate may raise risk of developing a serious infection and impair the

ability to fight off infections from bacteria, viruses, and fungus. Inform your physician about any frequent infections youhave. Included in this are infections that are minor (like cold sores or open cuts), sporadic (like herpes) and chronic (like persistent infections). When taking Diroximel fumarate, Fever, chills, sweats, muscle aches, coughing, shortness of breath, warm, red, or painful skin or sores on your body, diarrhoea, stomach pain, frequent, urgent, or painful urination are the common symptoms which are observed [18, 20].

References

1. https://go.drugbank.com/drugs/DB14783
2. Hauer L, Sellner J. Diroximel fumarate as a novel oral immunomodulating therapy for relapsing forms of multiple sclerosis: a review on the emerging data,2022:16:3915–3927.
3. MedlinePlus [Internet]. Available from: https://medlineplus.gov › druginfo › meds
4. Wikipedia [Internet]. Diroximel fumarate. Available from: https://en.wikipedia.org › wiki › Diroximel_fumarate
5. Jonasson E, Sejbaek T. Diroximel fumarate in the treatment of multiple sclerosis. Neurodegenerative Disease Management, 2021, 10(5).
6. Montes Diaz G, Hupperts R, Fraussen J, Somers V. Dimethyl fumarate treatment in multiple sclerosis: recent advances in clinical and immunological studies. Autoimmunity Reviews,2018:17(12):1240-1250.
7. Montalban X, Gold R, Thompson AJ, *et al*. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler,2018:24(2):96–120.
8. Blair HA. Dimethyl fumarate: a review in relapsing-remitting MS. Drugs,2019:79(18):1965–76.
9. Liseno J, Lager B, Miller C, Shankar SL, Mendoza JP, Lewin JB. Multiple sclerosis patients treated with Diroximel fumarate in the real-world setting have high rates of persistence and adherence. Neurol Ther,2021:10:352–357.
10. Wray S, Bergh FT, Wundes A, Arnold DL, Drulovic J, Jasinska E, *et al*. Efficacy and safety outcomes with Diroximel fumarate after switching from prior therapies or continuing on DRF: results from the Phase 3 EVOLVE-MS-1 Study. Adv Ther,2022:39:1820–1823.
11. Singer BA, Shafer SJ, Arnold DL, Bowen JD, LaGanke C, Chen H, *et al*. Diroximel fumarate and dimethyl fumarate demonstrate early clinical and radiological efficacy in relapsing-remitting multiple sclerosis. Neurology,2020:94(Supplement):15.
12. Liang G, Chai J, Ng HS, Tremlett H. Safety of dimethyl fumarate for multiple sclerosis: a systematic review and meta-analysis. Multiple Sclerosis and Related Disorders,2020:46:102566.
13. Prabhat V, Prem S. An overview of DRF in the treatment of multiple sclerosis. Research Journal of Pharmacy and Technology,2020:13(6):2993.
14. Faissner S, Gold R. Efficacy and safety of multiple sclerosis drugs approved since 2018 and future developments. CNS Drugs,2022:36:809–813.
15. Dobson R, Giovannoni G. Multiple sclerosis—a review. Eur J Neurol,2019:26(1):27–40.
16. Wang Y, Bhargava P. Diroximel fumarate to treat multiple sclerosis,2020:56(7):432-435.
17. Callegaria I, Derfuss T, Galli E. Update on treatment in multiple sclerosis. La Presse Medicale,2021:50(2):104068.
18. Wei W, Ma D, Li L, Zhang L. Progress in the application of drugs for the treatment of multiple sclerosis, 2021, 12.
19. Hauser SL, Cree BAC. Treatment of multiple sclerosis: a review. Am J Med,2020:133(12):1387.
20. Gaber T. Diroximel fumarate – a new twist for MS agent best seller. Progress in Neurology and Psychiatry,2022:26(3):8-9. Paik J. Diroximel fumarate in relapsing forms of multiple sclerosis: a profile of its use. CNS Drugs,2021:35:691–700.