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REVIEW ARTICLE

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Subcutaneous methotrexate-containing medicinal products — comparative studies of pharmaceutical form and immediate packaging

ABSTRACT

Despite the passage of time and the emergence of more drugs on the pharmaceutical market, methotrexate (MTX) is still considered the primary drug for the treatment of rheumatoid arthritis and other inflammatory rheumatic disorders. However, the best forms of MTX therapy are still being sought. Based on the available literature, subcutaneous MTX is preferred, especially when using higher doses, due to its better bioavailability and lower incidence of side effects. Nevertheless, some patients still prefer oral therapy. Therefore, it is important to make patients as comfortable as possible with injectable MTX, which can contribute to better cooperation. This paper presents the results from a comparative analysis of selected 15 mg pre-filled syringes (PFS) containing MTX available on the Polish market in terms of technological differences and product administration.

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KEY WORDS: methotrexate; rheumatic diseases; subcutaneous injections

INTRODUCTION

Methotrexate (MTX) is an established drug that has been used in many areas of medicine for decades. The first uses of MTX were in patients with cancer. Subsequently, the drug was also administered to rheumatology and dermatology patients. The mechanism of action of MTX is based on the inhibition of dihydrofolate reductase activity, which prevents the reduction of folic acid to its active metabolic derivative — this leads to inhibition of cell growth and diverting cells into the path of apoptosis. In addition, MTX also causes increased release of adenosine from adenine nucleotides, which contributes to the anti-inflammatory effect. This complex mechanism of action — immunomodulatory and anti-inflammatory — has been exploited to treat autoimmune diseases [1].

Despite the passage of time and the emergence of further immunosuppressive drugs on the pharmaceutical market, MTX is still considered the primary drug for the treatment of rheumatoid arthritis and other inflammatory rheumatic diseases — both because of its efficacy as monotherapy and in combination with biologic drugs. In addition, it is a drug with a well-established and favourable safety profile. The affordability of the therapy is also not insignificant. Therefore, the position of MTX in rheumatology still appears unthreatened [2, 3].

Based on the available literature, subcutaneous MTX is currently preferred, especially for higher doses. This is because subcutaneous MTX significantly reduces the incidence of nausea and diarrhoea compared with oral administration [4]. In addition, the bioavailability of oral compared to parenteral administration

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is lower, especially at doses above 15 mg [5]. Still, some patients prefer the oral form because of its convenience. This is especially true for elderly patients with limited dexterity. For this reason, the best forms of MTX therapy are still being sought. Therefore, post-authorisation studies provide information from actual medical practice and should be conducted throughout the drug's presence on the pharmaceutical market, as they provide valuable data for clinicians [6, 7].

This paper presents the results from a comparative analysis of the pharmaceutical form and unit immediate packaging of pre-filled syringes (PFS) of medicinal products containing MTX at a dose of 15 mg per unit package in terms of technological differences and product administration. The study was conducted by specialists from the Department of Drug Form Technology at the Medical University of Łódź, commissioned by Accord Healthcare Polska Sp. z o.o.

STUDY DESCRIPTION

The comparative analysis included selected MTX-containing preparations for subcutaneous injection available on the Polish market:
— Metex 50 mg/ml (15 mg/0.3 mL), 12 × 0.3 mL pre-filled syringes (Medac);
— Methofill 50 mg/ml (15 mg/0.3 mL), 8 × 0.3 mL pre-filled syringes (Accord Healthcare Polska Sp. z o.o.);
— Namaxir 15 mg, 4 × 0.38 mL pre-filled syringes (Teva, Actavis Group PTC ehf.);
— Tullex 15 mg, 12 × 0.4 mL pre-filled syringes (Egis Pharmaceuticals PLC).

The comparison of individual aspects of the pre-filled syringes concerned the following functional aspects:
— composition;
— packaging characteristics;
— comfort of administration.

The following research methodology was used to achieve the aim of the study:
— technological analysis of the composition of the tested injectable MTX in terms of the excipients used based on the analysis of the qualitative and quantitative composition of the tested medicinal products;
— testing of the physicochemical properties of the fluid contained in the pre-filled syringes: viscosity tests of the injection fluid and their correlation with the properties of the immediate packaging, testing of the pH and density of the fluid, texture analysis (hardness, adhesion, cohesion).
— examination of the immediate packaging in terms of convenience and comfort of use, particularly with regard to distance, the force of the plunger, length and colour of the pre-filled syringe flange, concentration/amount of active substance, which must be injected by the patient during a single injection, needle morphology and properties of the needle guard mechanism in terms of whether the needle is integrated into the pre-filled syringe and whether the needle retracts spontaneously after an injection;
— a model application was carried out using a texture analyser.

Table 1 shows the characteristics of the medicinal products studied.

Figure 1 shows the PFS assessed.

RESULTS

COMPOSITION

All the injectable medicinal products tested are based on a simple formulation with water as the solvent for injection. Sodium hydroxide and sodium chloride have been used to maintain the correct pH and osmoticity. Ebetrexat, Metex, Methofill and Namaxir have an identical qualitative composition.

Table 1. Characteristics of the medicinal products studied

Product name	Number of ampoules per packaging	Quantity of methotrexate in 1 mL of preparation [mg]	Quantity of mL per ampoule	Expiration date	Series	Storage temperature [°C]
Ebetrexat	1	20.00	0.75	November 2023	LX9680	25
Metex	12	50.00	0.30	April 2024	E220194AA	25
Methofill	1	50.00	0.30	September 2023	G2102286	30
Namaxir	4	39.47	0.38	April 2024	22E5023	25
Tullex	12	37.50	0.40	September 2024	222340	25

Figure 1. Assessed pre-filled syringes (PFS) containing methotrexate (MTX)

The exception is Tullex, which additionally contains hydrochloric acid. All medicinal products tested have very similar mean density and mean pH, which comply with the pharmacopoeial standards provided for liquids for injection. The values of the above differences are negligible and do not allow differentiation of the product technologies.

However, significant differences in drug concentrations were shown (Fig. 2).

The highest concentrations, i.e. the amount of MTX in 1 mL of the preparation in milligrams, i.e. 50 mg/ml, were found in Methofill and Metex. Ebetrexat had the lowest concentration, i.e. 20 mg/ml, while medium concentrations were found in Namaxir—39.47 mg/ml and Tullex—37.50 mg/ml. Due to the different drug concentrations, the preparations studied have different injection volumes needed to introduce the correct dose of the drug.

There was also a difference in the viscosity of the preparations (Fig. 3).

The mean value of structural viscosity of 1.083 mPa·s for Methofill is in the middle of the values obtained for the other products tested. According to the researchers, high viscosity could hinder the application of the product, while too low a viscosity could result in product leakage.

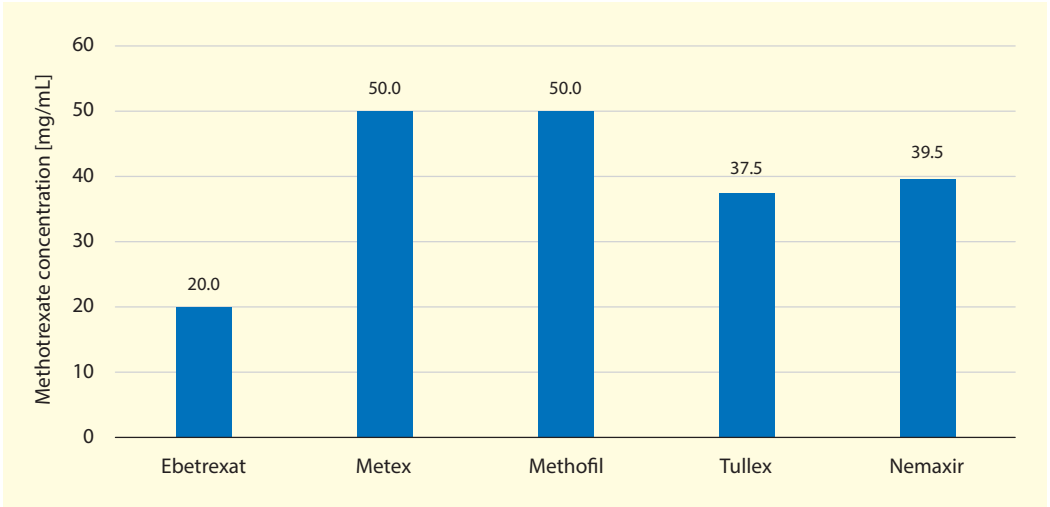

Figure 2. Concentrations of methotrexate in the studied medicinal products

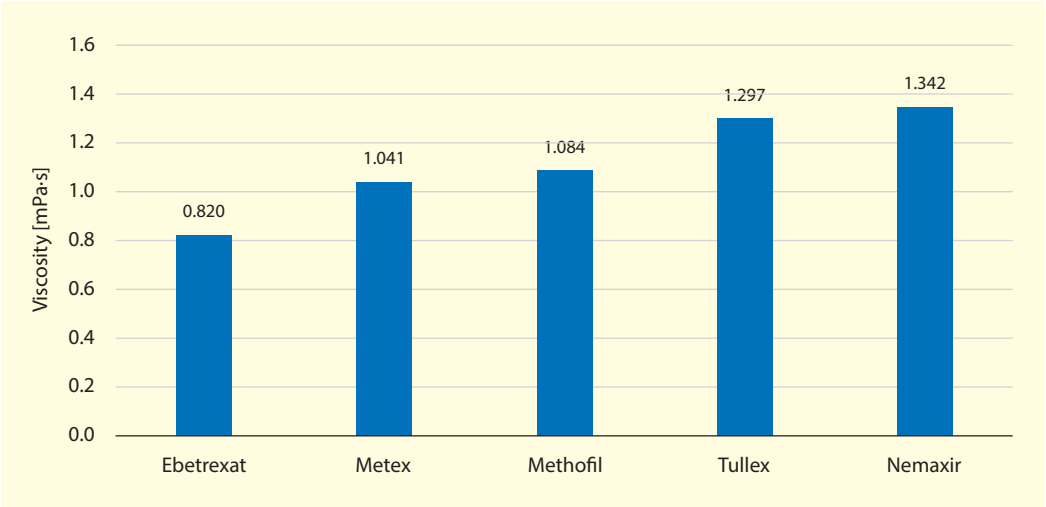

Figure 3. Viscosity of the tested products

The storage conditions are also noteworthy. All tested injectable MTX solutions have a storage temperature below 25°C. Only Methofill can be stored at a higher temperature — below 30°C. This is advantageous for preserving the shelf life and the patient's comfort in distribution and administration, as even exceeding the storage temperature above 25°C does not pose a risk of losing the drug's shelf life.

PACKAGING CHARACTERISTICS

All tested pre-filled syringes are contained in plastic extrusions for stable storage of the products. However, they differ in the covering material and the nature and type of printing. The most legible printing in terms of type, size, font colouring, and precise information is provided on the immediate packaging of the PFS (i.e. the trade name of the product, the name of the active substance, the PFS volume, the concentration, the dosage frequency, the batch number, the expiry date, and the name of the marketing authorisation holder) were noted by the researchers for Methofill. The print is legible and varied in colour. The colour differentiation (red marking) relates to the important information on the dosage regimen of the medicinal product, i.e. once a week only. The reverse side of the PFS immediate packaging of Metex and Tullex contains information such as the product trade name, name of the active substance, concentration, dosing frequency, batch number, expiry date, and name of the marketing authorisation holder. The reverse side of Namaxir's immediate packaging contains the expiration date and batch number. Only Ebetrexat is packaged in a transparent extrusion with no markings.

The tested PFS differ in the type of labelling (size, colour variation, font size, colour of the label, i.e. white or colourless) affixed directly to the PFS. Only Methofill has an all-white label, printed in a varied colour font, which, according to the researchers, may make it easier to identify the information on the label (such as the name of the medicinal product, concentration, drug dose, PFS volume, expiry date, batch number, name of the marketing authorisation holder, dosage regimen). Information on the dosage regimen (i.e. once a week) is marked in red, which the researchers believe may minimise the risk of potential dosing errors.

COMFORT OF ADMINISTRATION

The injectable forms of the drug studied have different amounts of injection volume needed to introduce 15 mg of MTX. This ranges from 0.3 mL to 0.75 mL. According to the researchers, due to the nature of both intramuscular administration and any injection, the less fluid to be injected, the better the patient's comfort with the drug in terms of potential pain. Ebetrexat has the largest volume of injection fluid, i.e. 0.75 mL. The smallest volume of injection fluid per PFS was found in Methofill and Metex, i.e. 0.3 mL. In addition, the volume (in millilitres) of the preparation injected into the body upon a 1 mm movement of the pre-filled syringe plunger is the smallest for Methofill. Moving the plunger of the Methofill PFS by 1 mm results in the injection of 0.019405 mL of the preparation, which, according to the researchers, may

be related to the patient's comfort during the performance of the injection—the less the preparation, the lower the level of discomfort associated with the injection may be. At the same time, according to the researchers, the smaller the amount of preparation administered by moving the plunger, the more precise and less painful the drug administration can be.

The PFS tested required different forces to move the plunger and perform the injection. The differences are due to the different design of each pre-filled syringe. The Methofill pre-filled syringe also showed the largest plunger usable area, i.e. 232.5 mm^2. The products with the smallest plunger usable area are Namaxir—77.87 mm^2 and Metex—74.62 mm^2. However, a certain dominant force range of 2.62655–2.97295 mN was observed for the PFS with Ebetrexat, Methofill and Tullex. What sets Methofill apart is the large, ergonomically curved handle with a fluted surface, which the researchers believe can prevent fingers from slipping off during injection, both from the handle and the plunger, increasing patient comfort and safety.

For this type of injection, the needle safety feature that protects against injury after the injection is also important. Three products have a passive needle guard mechanism, whereby the needle retracts automatically into the PFS body after the injection has been performed: Methofill, Namaxir and Tullex.

CONCLUSIONS

Recently, the advantage of using subcutaneous MTX has been highlighted due to better bioavailability and a lower incidence of side effects. Nevertheless, some patients still prefer oral therapy. Therefore, it is essential to ensure that patients are sufficiently comfortable with injectable MTX, which can contribute to better cooperation and safer treatment. There is currently a large selection of MTX preparations available on the Polish market in the form of convenient pre-filled syringes, which should ensure an appropriate choice of product tailored to the patient's preferences.

AUTHOR CONTRIBUTIONS

D.S. and W.S. are co-authors of this article.

CONFLICT OF INTEREST AND FUNDING

The study was conducted by specialists from the Department of Drug Form Technology, Medical University of Lodz, commissioned by Accord Healthcare Polska Sp. z o. o.

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