Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Diclofenac Sodium 25 mg Gastro-resistant Tablets
Diclofenac Sodium 50 mg Gastro-resistant Tablets

(Diclofenac sodium)

UK Licence Numbers: PL 21880/0193-0194

Medreich Plc.

LAY SUMMARY

Diclofenac Sodium 25 mg Gastro-resistant Tablets
Diclofenac Sodium 50 mg Gastro-resistant Tablets

(diclofenac sodium, gastro-resistant tablet, 25 mg and 50 mg)

This is a summary of the Public Assessment Report (PAR) for Diclofenac Sodium 25 mg Gastro-resistant Tablets (PL 21880/0193) and Diclofenac Sodium 50 mg Gastro-resistant Tablets (PL 21880/0194). It explains how Diclofenac Sodium 25 mg and 50 mg Gastro-resistant Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Diclofenac Sodium 25 mg and 50 mg Gastro-resistant Tablets.

The products will be referred to as Diclofenac Tablets throughout the remainder of this public assessment report (PAR).

For practical information about using Diclofenac Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Diclofenac Tablets and what are they used for?
Diclofenac Tablets are a 'generic medicine'. This means that Diclofenac Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Voltarol Tablets 25 mg and 50 mg (Novartis Pharmaceuticals UK Limited).

Diclofenac Tablets relieve pain, reduce swelling and ease inflammation in conditions affecting the joints, muscles and tendons including:

- Rheumatoid arthritis, osteoarthritis, acute gout, ankylosing spondylitis
- Backache, sprains and strains, soft tissue sports injuries, frozen shoulder, dislocations and fractures
- Tendonitis, tenosynovitis, bursitis
- Pain and inflammation associated with dental and minor surgery.

In addition to the above, Diclofenac Sodium 25 mg Gastro-resistant Tablets are also used to treat juvenile chronic arthritis in children.

How do Diclofenac Tablets work?
This medicine contains the active ingredient diclofenac sodium which is part of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDS). NSAIDS are used to reduce pain and inflammation.

How are Diclofenac Tablets used?
The pharmaceutical form of Diclofenac Tablets is a gastro-resistant tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The tablets should be swallowed whole preferably with a drink of water, before or with food. **Do not** crush or chew the tablets as the tablets have been coated with a substance, which allows them to pass through the stomach before dissolving. It is important that the coating is not damaged by chewing.

Dosage
The patient's doctor will decide their dose, as it depends on the patient's condition.

For Diclofenac Sodium 25 mg Gastro-resistant Tablets:
Adults and children over 12:
A typical dose is 75 mg to 150 mg daily divided into two or three doses

Elderly and patients with kidney problems:
The patient's doctor may advise them to take a dose that is lower than the usual adult dose if the patient is elderly.

Children aged 1-12years:
Doses vary with the age and weight of the child. The usual dose is 1 mg to 3 mg per kilogram of body weight a day. This is usually divided into two or three separate doses.

The doctor may also prescribe another drug to protect the stomach to be taken at the same time, particularly if the patient has had stomach problems before, or if they are elderly, or taking certain other drugs as well.

For Diclofenac Sodium 50 mg Gastro-resistant Tablets:
Adults:
A typical dose is 75 mg to 150 mg daily divided into two or three doses.

Elderly and patients with kidney problems:
The patient's doctor may advise them to take a dose that is lower than the usual adult dose if they are elderly.

Children:
Diclofenac Sodium 50 mg Gastro-resistant Tablets are not recommended for children.

The doctor may also prescribe another drug to protect the stomach to be taken at the same time, particularly if the patient has had stomach problems before, or if they are elderly, or taking certain other drugs as well.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Diclofenac Tablets have been shown in studies?
Because Diclofenac Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Voltarol Tablets 25mg and 50 mg (Novartis Pharmaceuticals UK Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Diclofenac Tablets?
Because Diclofenac Tablets are a generic medicine, their benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Diclofenac Tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Diclofenac Tablets approved?
It was concluded that, in accordance with EU requirements, Diclofenac Tablets have been shown to have comparable quality and to be bioequivalent to Voltarol Tablets 25mg and 50 mg (Novartis Pharmaceuticals UK Limited). Therefore, the MHRA decided that, as for Voltarol Tablets 25mg and 50 mg (Novartis Pharmaceuticals UK Limited); the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Diclofenac Tablets?
A risk management plan (RMP) has been developed to ensure that Diclofenac Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Diclofenac Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Diclofenac Tablets
The Marketing Authorisations for Diclofenac Tablets were granted in the UK on 28 June 2016.

The full PAR for Diclofenac Tablets follows this summary.

For more information about use of Diclofenac Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Medreich Plc, marketing authorisations for the medicinal product Diclofenac Tablets (PL 21880/0193-0194).

Diclofenac Tablets are Prescription Only Medicines (POM) indicated for:
Adults and Elderly:
Relief of all grades of pain and inflammation in a wide range of conditions, including:

i. arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,
ii. acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,
iii. other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

In addition to the above, Diclofenac Sodium 25 mg Gastro-resistant Tablets are indicated for juvenile chronic arthritis in children aged 1 to 12 years of age.

Diclofenac Sodium 50 mg Gastro-resistant Tablets are **not** recommended for use in **children**.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products which have been authorised in the Community for at least 10 years for these applications are Voltaren 25 mg and 50 mg Gastro-resistant Tablets (RVG07003 and RVG07008), authorised to Novartis Healthcare A/S, Netherlands since 15 October 1976. The equivalent reference products in the UK are Voltarol Tablets 25mg and 50 mg (PL 00101/0476-0477; Novartis Pharmaceuticals UK Limited). The UK reference products were originally authorised under PL 00001/0036 (25 mg) and PL 00001/0082 (50 mg) to Ciba-Geigy Plc in 1978 and 1979 respectively. Both licences then went through a change of ownership on 11 July 1997 from Ciba-Geigy Plc to Novartis Pharmaceuticals UK Limited. The reference products PL 00001/0036 and PL 0001/0082 were based on a full dossier (New Active Substance).

Bioequivalence has been investigated against the UK reference product Voltarol Tablets 50 mg (PL 00101/0477) authorised to Novartis Pharmaceuticals UK Limited. This reference product is considered acceptable for the purposes of demonstration of bioequivalence as it belongs to the same global marketing authorisation as Voltaren 50 mg Gastro-resistant Tablets, RVG07008, authorised in the Netherlands.

Diclofenac is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

Results from two bioequivalence studies were submitted to support these applications conducted under fed and fasting conditions. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Diclofenac Tablets outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

Each enteric coated tablet contains 25 mg or 50 mg of the active ingredient diclofenac sodium. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, povidone (K30), maize starch, sodium starch glycolate (Type A), microcrystalline cellulose (PH-102), colloidal anhydrous silica, magnesium stearate, purified talc, hypromellose, macrogolglycerol hydroxystearate, iron oxide yellow (E172), titanium dioxide (E171), methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30% and triethyl citrate. The 50 mg strength tablets also contain iron oxide red (E172).

Both strengths of the finished product are packed into:
Aluminium / polyvinyl chloride (PVC) blister packs of 28 and 84 tablets.
Alu / PVC/polyvinlidene chloride (PVdC) blister packs of 28 and 84 tablets.

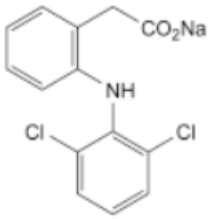
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

Diclofenac sodium

INN:	Diclofenac sodium
Chemical name:	Sodium 2-[(2, 6-dichlorophenyl)amino]phenyl] acetate.

Structure:



Molecular formula:	$C_{14}H_{10}Cl_2NNaO_2$
Molecular weight:	318.1
Appearance:	White or slightly yellowish, slightly hygroscopic, crystalline powder.
Solubility:	Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

Diclofenac sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, diclofenac sodium, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, gastro-resistant tablets containing 25 mg or 50 mg diclofenac sodium per tablet that are generic versions of the reference products Voltarol Tablets 25mg and 50 mg (Novartis Pharmaceuticals UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide yellow (E172) and iron oxide red (E172), which are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of diclofenac sodium are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Diclofenac Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of diclofenac sodium is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of diclofenac sodium

Based on the data provided, Diclofenac Tablets can be considered bioequivalent to Voltarol Tablets 25mg and 50 mg (Novartis Pharmaceuticals UK Limited).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted results from the following bioequivalence studies:

STUDY 1

An open label, balanced, randomised, two-treatment, two-sequence, four period, full replicate, cross-over, single-dose oral bioequivalence study to compare the pharmacokinetics of the applicant's test product Diclofenac Sodium 50 mg Gastro-resistant Tablets (Medreich Plc, UK) versus the reference product, Voltarol Tablets 50 mg (Novartis Pharmaceuticals UK Limited), in healthy adult subjects under fasting conditions.

Following an overnight fast of at least 10 hours, subjects were dosed with a single oral dose of either the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was at least 10 days. The pharmacokinetic results are presented below:

Table: Least square mean, ratios and 90% Confidence Interval for diclofenac (fasting conditions):

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vsR	Intra Subject CV (%)	ISCV (%) Reference	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%				
C_{max} (ng/mL)	1567.718	1508.722	103.91	98.08-110.09	26.0	15.8	100
$AUC_{0\rightarrow t}$ (hr. ng/mL)	1948.843	1936.367	100.64	97.63-103.75	13.5	6.8	100
$AUC_{0\rightarrow\infty}$(hr. ng/mL)	1982.225	1964.974	100.88	97.89-103.96	13.3	6.8	100

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from zero to t hours
C_{max} maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for diclofenac (administered under fasting conditions) lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Voltarol Tablets 50 mg (Novartis Pharmaceuticals UK Limited).

As the 25 mg, 50 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 50 mg tablet strength can be extrapolated to the 25 mg strength tablet.

STUDY 2
An open label, balanced, randomised, two-treatment, two-sequence, four period, full replicate, cross-over, single-dose oral bioequivalence study to compare the pharmacokinetics of the applicant's test product Diclofenac Sodium 50 mg Gastro-resistant Tablets (Medreich Plc, UK) versus the reference product, Voltarol Tablets 50 mg (Novartis Pharmaceuticals UK Limited), in healthy adult subjects under fed conditions.

Following an overnight fast of at least 10 hours, and exactly 30 minutes after serving a high fat, high calorie breakfast, subjects were dosed with a single oral dose of either the test or the reference product with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 24 hours after each administration. The washout period between the treatment phases was at least 14 days. The pharmacokinetic results are presented below:

Table: Least square mean, ratios and 90% Confidence Interval for diclofenac (fed state):

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vsR	Intra Subject CV (%)	ISCV for Reference (%)	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%				
C_{max} (ng/mL)	1296.547	1360.255	95.32	86.30-105.27	38.5	27.3	98
AUC_{0-t} (hr. ng/mL)	2007.457	2034.070	98.69	94.49-103.08	16.4	13.4	100
$AUC_{0-\infty}$ (hr. ng/mL)	2082.932	2111.460	98.65	94.51-102.97	15.7	11.2	100

AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from zero to t hours
C_{max} maximum plasma concentration

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and Cmax values for diclofenac (administered in the fed state) lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Voltarol Tablets 50 mg (Novartis Pharmaceuticals UK Limited).

As the 25 mg, 50 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 50 mg tablet strength can be extrapolated to the 25 mg strength tablet.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for these applications.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Diclofenac Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	• Gastrointestinal toxicity including perforation, ulceration and bleeding (PUB) • Hypersensitivity/ allergic reactions, including anaphylactic and anaphylactoid reactions; bronchospasm in patients with asthma; asthma attacks, angioedema, urticarial or acute rhinitis in patients with prior hypersensitivity to ibuprofen, other NSAIDs or aspirin. • Arterial thrombotic events (myocardial infarction, stroke) • Cardiac failure, hypertension • Bleeding (inhibition of platelet function) • Blood dyscrasia including agranulocytosis and aplastic anaemia • Renal toxicity • Hepatitis, hepatic necrosis and hepatic failure • Serious skin reactions including Stevens Johnson syndrome and Toxic Epidermal Necrolysis • Developmental and maternal toxicity during pregnancy • Use during breast-feeding • Hyperkalaemia with concurrent use of potassium sparing diuretics, ciclosporin, tacrolimus or trimethoprim
Important potential risks	• Aseptic meningitis in patients with systemic lupus erythematosus (SLE) or other connective tissue disease • Impairment of female fertility
Missing information	• Use in patients with mild-moderate hepatic impairment • Use in patients with mild-moderate renal impairment

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with diclofenac sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:

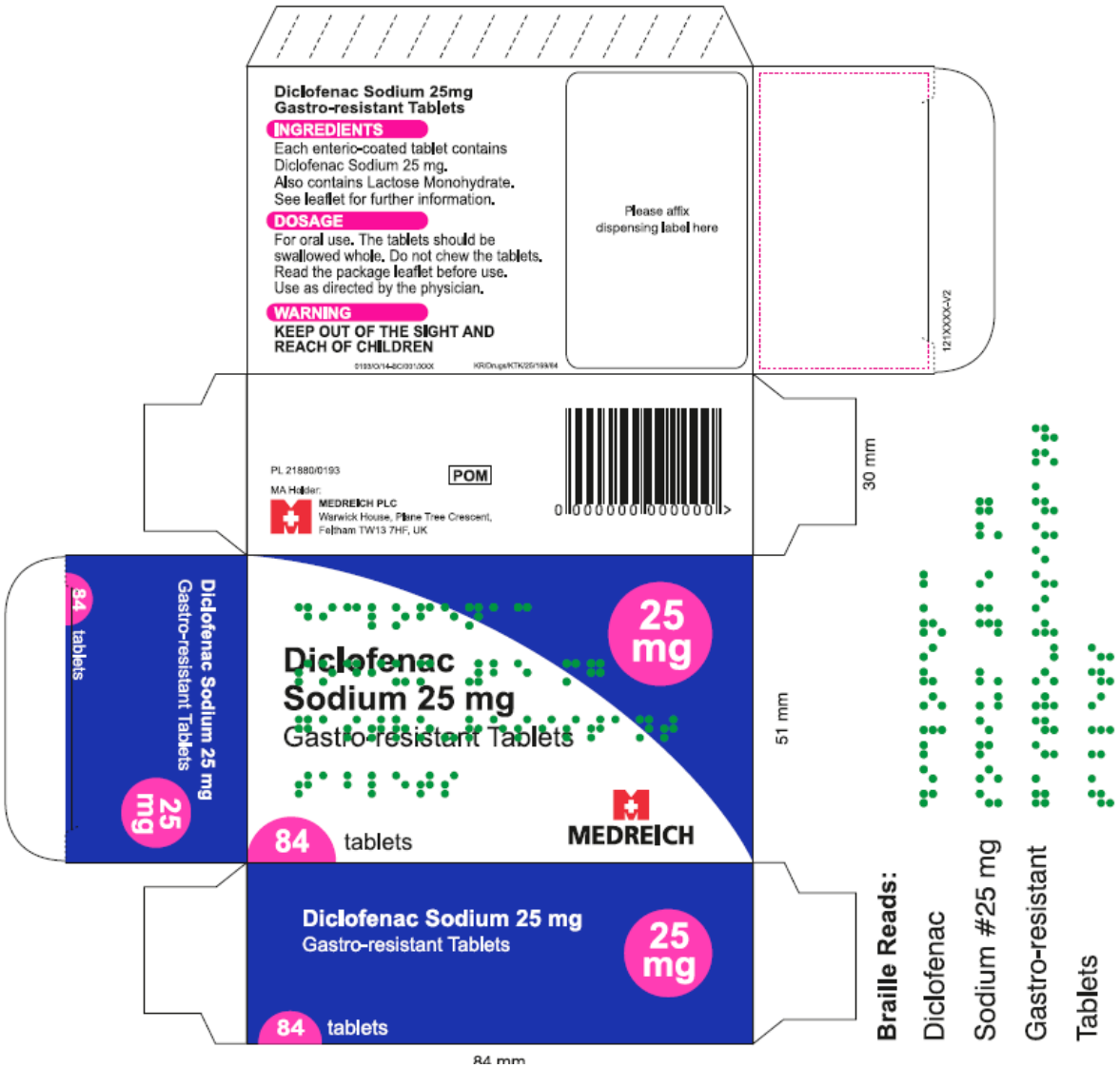
Braille Reads:

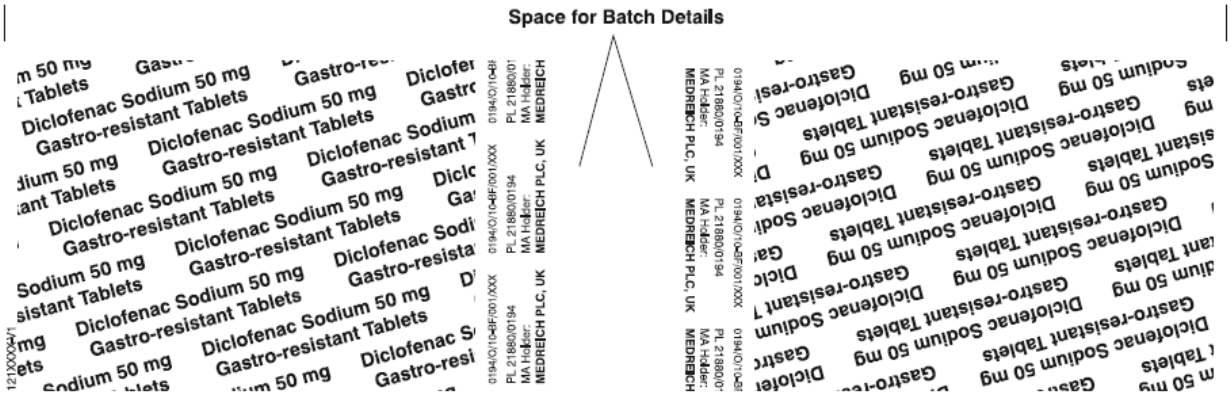
Diclofenac

Sodium #25 mg

Gastro-resistant

Tablets





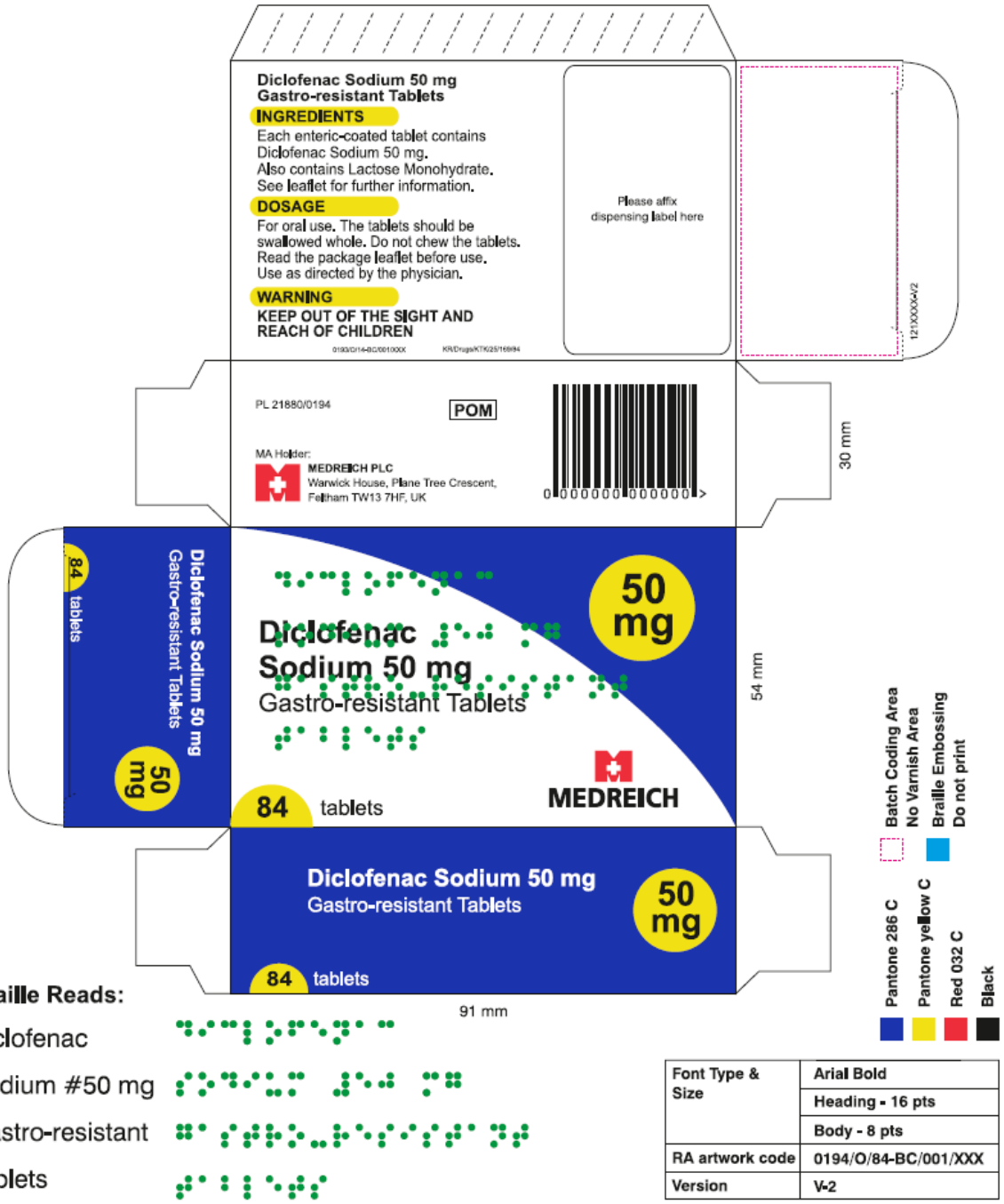
Braille Reads:

Diclofenac

Sodium #50 mg

Gastro-resistant

Tablets



Braille Reads:

Diclofenac

Sodium #50 mg

Gastro-resistant

Tablets

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	Body - 8 pts
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Version	V-2