



# **Public Assessment Report**

## **National Procedure**

**Leflunomide 10 mg film-coated tablets**  
**Leflunomide 15 mg film-coated tablets**  
**Leflunomide 20 mg film-coated tablets**

**leflunomide**

**PL 16363/0724-0726**

**Milpharm Limited**

## LAY SUMMARY

### Leflunomide 10, 15 and 20 mg film-coated tablets leflunomide

This is a summary of the Public Assessment Report (PAR) for Leflunomide 10, 15 and 20 mg film-coated tablets. It explains how these products 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 these products.

These products will be referred to as Leflunomide in this lay summary for ease of reading.

For practical information about using Leflunomide, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

#### **What are leflunomide and what are they used for?**

The applications for Leflunomide 10 and 20 mg film-coated tablets are for generic medicines. This means these medicines are the same as, and considered interchangeable with, reference medicines already authorised in the European Union (EU) called Arava 10 mg and 20 mg film coated tablets.

The application for Leflunomide 15 mg film-coated tablets is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Arava 10 mg and 20 mg film coated tablets.

Leflunomide belongs to a group of medicines called anti-rheumatic medicines. It contains the active substance leflunomide. Leflunomide is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis.

#### **How does leflunomide work?**

The active substance in Leflunomide, is an immunosuppressant. It reduces inflammation by reducing the production of immune cells called 'lymphocytes', which are responsible for inflammation. Leflunomide does this by blocking an enzyme called 'dihydroorotate dehydrogenase', which is necessary for the lymphocytes to multiply. With fewer lymphocytes, there is less inflammation, helping to control the symptoms of arthritis.

#### **How is leflunomide used?**

The pharmaceutical form of this medicine is film-coated tablets and the route of administration is by mouth (oral).

The usual starting dose of Leflunomide is 100 mg once daily for the first three days. After this, most patients need a dose of:

- for rheumatoid arthritis: 10 to 20 mg Leflunomide once daily, depending on the severity of the disease
- for psoriatic arthritis: 20 mg Leflunomide once daily.

**The tablet should be swallowed whole and with plenty of water.** It may take about 4 weeks or longer until the patient starts to feel an improvement in their condition. Some patients may feel further improvements after 4 to 6 months of therapy.

Patients will normally take Leflunomide over long periods of time.

If the patient forgets to take a dose, the patient should take it as soon as they remember, unless it is nearly time for the next dose. Patients should not take a double dose to make up for a forgotten dose.

For further information on how Leflunomide is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

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

### **What benefits of leflunomide have been shown in studies?**

Because Leflunomide 10 and 20 mg film-coated tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Because Leflunomide 15 mg film-coated tablets are a hybrid medicine, studies in healthy volunteers consist of tests to determine that they are bioequivalent to an equal dose of the reference medicine.

### **What are the possible side effects of leflunomide?**

For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Leflunomide 10 and 20 mg film-coated tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Because Leflunomide 15 mg film-coated tablets are a hybrid medicine and are bioequivalent to an equal dose of the reference medicine, their benefits and possible side effects are taken as being the same as the reference medicine.

### **Why was leflunomide approved?**

It was concluded that Leflunomide 10, 15 and 20 mg film-coated tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, 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 leflunomide?**

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Leflunomide. The RMP details the important risks of leflunomide, how these risks can be minimised, any uncertainties about leflunomide (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for leflunomide:

**Important identified risks**

- Hepatic reactions
- Blood cytopenia
- Severe skin reactions
- Infections
- Interstitial lung disease
- Teratogenicity
- Hypertension
- Concomitant use of other DMARDs (methotrexate)

**Important potential risks**

- Male-mediated foetal toxicity
- Lymphoproliferative disorders
- Progressive multifocal leukoencephalopathy
- Renal failure
- Peripheral neuropathy
- Risk of interaction with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptives

**Missing information**

- Use in children
- Concomitant use of biologic DMARDs

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of leflunomide are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals. Additional risk minimisation measures for healthcare professionals concerning important identified safety concerns have been agreed.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and these documents are satisfactory.

**Other information about leflunomide**

Marketing Authorisations for leflunomide were granted in the United Kingdom (UK) consisting of England, Scotland, Wales), and Northern Ireland on 5 April 2022.

The full PAR for Leflunomide film-coated tablets follows this summary.

This summary was last updated in June 2022.

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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) considered that the applications for Leflunomide 10, 15 and 20 mg film-coated tablets (PL 16363/0724-0726) could be approved.

The products are approved for the following indications:

Leflunomide is indicated for the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.

### Mechanism of action

A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.

The applications for Leflunomide 10 and 20 mg film-coated tablets were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Arava 10 mg and 20 mg film coated tablets, that have been licensed within the EU for a suitable time, in line with the legal requirements.

The application for Leflunomide 15 mg film-coated tablets was approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator products, Arava 10 mg and 20 mg film coated tablets that have been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for hybrid and generic medicinal products of suitable reference products.

Data from **two** bioequivalence studies were submitted with these applications. These studies were conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK), consisting of England, Scotland and Wales, and Northern Ireland (NI) on 5 April 2022.

## II QUALITY ASPECTS

### II.1 Introduction

The active substance is Leflunomide.

#### Leflunomide 10 mg film-coated tablets

Each film-coated tablet contains 10 mg of leflunomide.

#### Leflunomide 15 mg film-coated tablets

Each film-coated tablet contains 15 mg of leflunomide.

#### Leflunomide 20 mg film-coated tablets

Each film-coated tablet contains 20 mg of leflunomide.

#### Leflunomide 10 mg and 15 mg film-coated tablets

The other ingredients are: lactose monohydrate, maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, glyceryl monocaprylocaprate and sodium laurilsulfate.

#### Leflunomide 20 mg film-coated tablets

The other ingredients are: lactose monohydrate, maize starch, povidone, crospovidone, silica colloidal anhydrous, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide, glyceryl monocaprylocaprate, sodium laurilsulfate and iron oxide yellow NF.

The finished products are packaged in white opaque round HDPE containers with white opaque polypropylene closures. Each HDPE container contains 1g molecular sieve as desiccant. Pack size: 30 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

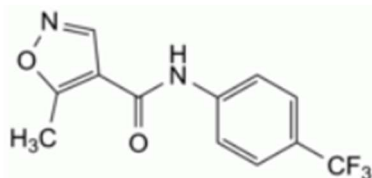
### II.2 ACTIVE SUBSTANCE

#### rINN: Leflunomide

Chemical Name: 5-Methyl-*N*-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide.

Molecular Formula: C<sub>12</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>

Chemical Structure:



Molecular Weight: 270.2

Appearance: White or almost white powder.

Solubility: Practically insoluble in water, freely soluble in methanol, sparingly soluble in methylene chloride.

Leflunomide is the subject of a European Pharmacopoeia monograph.

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

### **II.3 DRUG PRODUCTS**

#### **Pharmaceutical development**

A satisfactory account of the pharmaceutical development has been provided. Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

These products do not contain or consist of genetically modified organisms (GMO).

#### **Manufacture of the products**

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product(s), along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

#### **Finished Product Specifications**

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

#### **Stability**

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years without special storage conditions, is acceptable.

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**

The grant of marketing authorisations is recommended.

### III NON-CLINICAL ASPECTS

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of leflunomide is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

#### III.2 Pharmacology

No new pharmacology data were provided and none were required for these applications.

#### III.3 Pharmacokinetics

No new pharmacokinetic data were provided and none were required for these applications.

#### III.4 Toxicology

No new toxicology data were provided and none were required for these applications.

#### III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this these are hybrid and generic applications of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

#### III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisations is recommended.

### IV CLINICAL ASPECTS

#### IV.1 Introduction

In accordance with the regulatory requirements, data from two bioequivalence studies have been submitted with these applications. These studies were conducted in-line with current Good Clinical Practice (GCP).

#### IV.2 Pharmacokinetics

In support of the applications, the applicant submitted the following.

##### **10 mg bioequivalence study (20-061)**

An open-label, balanced, randomised, single-dose, two-treatment, single-period, parallel oral bioequivalence study of Leflunomide Tablets 10 mg versus the reference product Arava (leflunomide) 10mg film-coated tablets, in healthy, adult, human male subjects under fasting conditions.

After an overnight fast of at least 10.00 hours, a single dose of the reference product or the test product was administered orally to each subject with water. Blood samples were collected at 0.00 hour pre-dose, and up to 72.00 hours post-dose.

A parallel design has been chosen for the study because of the long elimination half-life of the active metabolite A771726 (teriflunomide). According to the SmPC of the reference product, the half-life of the parent drug is approximately 14 days.

A summary of the pharmacokinetic results are presented below:

Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean			Lower	Upper
	Test Product (T)	Reference Product (R)	T/R (%)		
$C_{max}$ (ng/mL)	1185.6041	1176.1174	100.81	95.65	106.25
$AUC_{0-72h}$ (ng.hr/mL)	61968.6107	62008.5645	99.94	95.07	105.05

### Pharmacokinetic study 0330-19 (20 mg)

An open label, balanced, randomized, two-treatment, single period, parallel, single-dose, oral bioequivalence study of leflunomide tablets 20 mg versus Arava® (leflunomide) tablets 20 mg, in normal, healthy adult human male subjects under fasting conditions.

After an overnight fast of at least 10 hours, a single oral dose (20 mg) of either the test product or the reference product was administered to the subjects with water. Blood samples were collected at pre-dose (0.000 hour) and up to 72.000 hours following administration.

A parallel design has been chosen for the study because of the long elimination half-life of the active metabolite A771726 (teriflunomide). According to the SmPC of the reference product, the half-life of the parent drug is approximately 14 days.

A summary of the pharmacokinetic results are presented below:

Parameters	Geometric Least Squares Means			90% Confidence Interval	Inter Subject CV (%)	Power (%)
	Test Product-T (N = 36)	Reference Product-R (N = 36)	Ratio (T/R)%			
$\ln C_{max}$	2435.431	2384.973	102.1	96.72 - 107.81	13.9	100.0
$\ln AUC_{0-72}$	120959.626	122061.018	99.1	94.46 - 103.97	12.3	100.0

According to the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference products.

As the additional 15mg strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline the results and conclusions from the bioequivalence studies on the other product strengths can be extrapolated to this strength.

### IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted for these applications and none were required.

### IV.4 Clinical efficacy

No new efficacy data have been submitted for these applications and none were required.

#### **IV.5 Clinical safety**

With the exception of the safety data from the clinical studies submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these data.

#### **IV.6 Risk Management Plan (RMP)**

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional risk minimisation measures have been proposed which consist of Physician Educational Pack (Physician leaflet, SmPC, Patient information sheet). This is acceptable.

#### **IV.7 Discussion on the clinical aspects**

The grant of marketing authorisations is recommended for these applications.

### **V USER CONSULTATION**

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation with target patient groups, in accordance with legal requirements, on the basis of a bridging report making reference to Metoprolol Aurobindo 50 mg & 100 mg film-coated tablets (SE/H/1201/01-02/DC). The bridging report submitted by the applicant is acceptable.

### **VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with leflunomide is considered to have demonstrated the therapeutic value of the products.

The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

In accordance with legal requirements, the current approved versions of the SmPCs and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



Each film-coated tablet contains **10 mg** of leflunomide.

Contains Lactose.

See the package leaflet for further information.

Oral use.

Read the package leaflet before use.

Keep out of the sight and reach of children.

**10 mg**

**Leflunomide film-coated tablets**

leflunomide

30 film-coated tablets

**Milpharm**

**10 mg**

**POM**

PL 16363/0724

Milpharm Limited

HA4 6QD

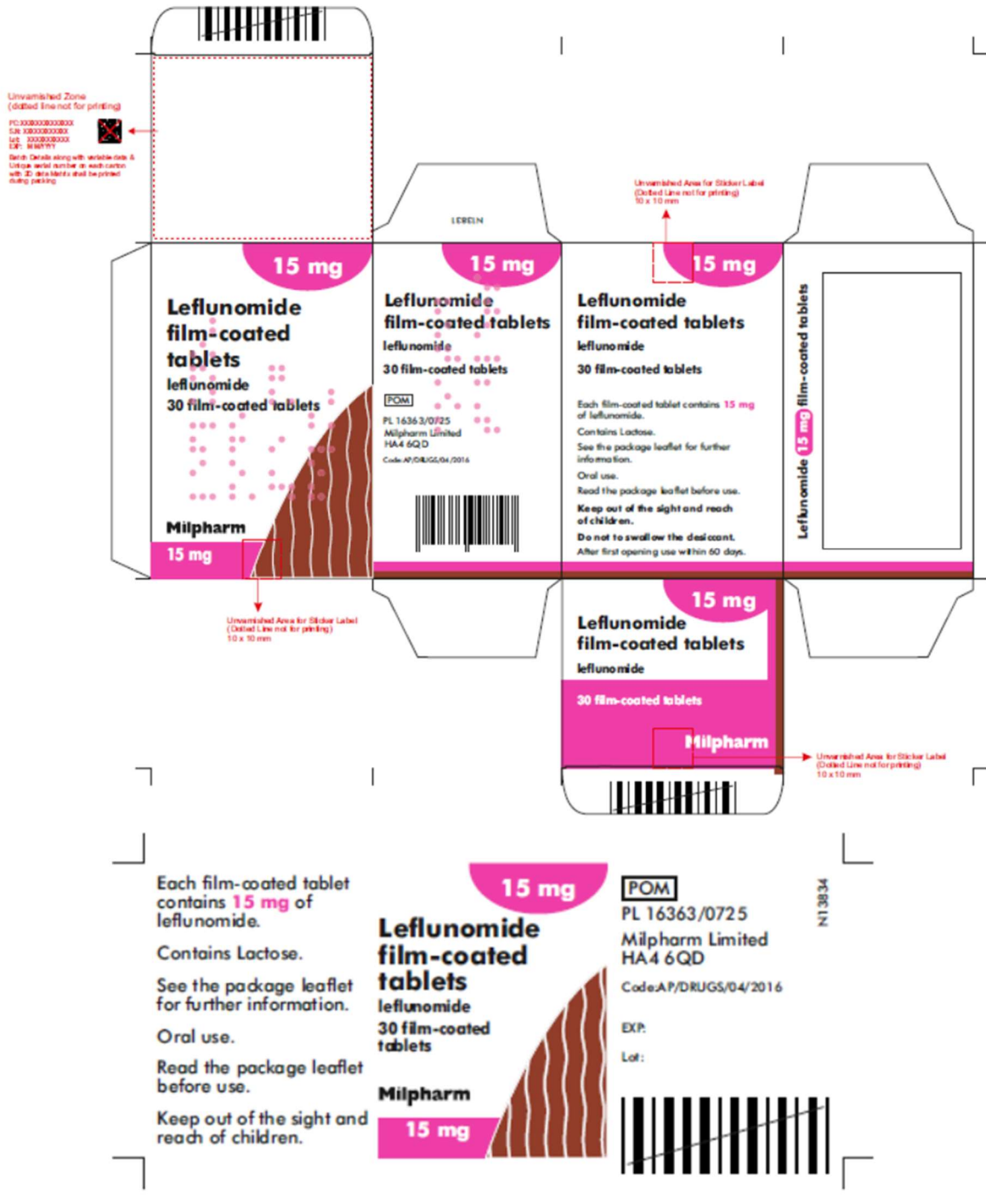
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**TABLE OF CONTENT OF THE PAR UPDATE**

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

<b>Application type</b>	<b>Scope</b>	<b>Product information affected</b>	<b>Date of grant</b>	<b>Outcome</b>	<b>Assessment report attached Y/N</b>