Public Assessment Report

Decentralised Procedure

Montelukast Paediatric 5mg chewable tablets

(montelukast sodium)

Procedure No: UK/H/5411/002/DC

UK Licence No: PL 36390/0153

Cipla (EU) Limited
LAY SUMMARY

Montelukast Paediatric 5 mg chewable tablets
(montelukast sodium, chewable tablets, 5 mg)

This is a summary of the Public Assessment Report (PAR) for Montelukast Paediatric 5 mg chewable tablets (PL 36390/0153; UK/H/5411/002/DC). It explains how Montelukast Paediatric 5 mg chewable 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 Montelukast Paediatric 5 mg chewable tablets.

For practical information about using Montelukast Paediatric 5 mg chewable tablets patients should read the package leaflet or contact their doctor or pharmacist.

Montelukast Paediatric 5 mg chewable tablets may be referred to as Montelukast Paediatric 5 mg in this report.

What is Montelukast Paediatric 5 mg and what is it used for?
Montelukast Paediatric 5 mg is a medicine that contains the active substance montelukast (as montelukast sodium). Montelukast Paediatric 5 mg is used to treat asthma by preventing asthma symptoms during the day and night.

Asthma is a long-term disease. Asthma includes:

- Difficulty breathing because of narrowed airways. This narrowing of airways worsens and improves in response to various conditions.
- Sensitive airways that react to many things, such as cigarette smoke, pollen, cold air, or exercise.
- Swelling (inflammation) in the lining of the airways.

Symptoms of asthma include: coughing, wheezing, and chest tightness.

Montelukast Paediatric 5 mg is used in patients 6 to 14 year old:

- for the treatment of asthma of patients who are not adequately controlled on their medication and need additional therapy
- as an alternative treatment to inhaled corticosteroids for patients who have not recently taken oral corticosteroids for their asthma and have shown that they are unable to use inhaled corticosteroids.
- to help prevent the narrowing of airways triggered by exercise.

Montelukast Paediatric 5 mg is a ‘generic’ medicine. This means that Montelukast Paediatric 5 mg is similar to a reference medicine already authorised in the European Union (EU) called Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme Limited).

How does Montelukast Paediatric 5 mg work?
Montelukast Paediatric 5 mg contains the active substance montelukast. Montelukast Paediatric 5 mg is a leukotriene receptor antagonist that blocks substances called leukotrienes. Leukotrienes cause narrowing and swelling of airways in the lungs. By blocking leukotrienes, Montelukast Paediatric 5 mg improves asthma symptoms and helps control asthma.

How is Montelukast Paediatric 5 mg used?
Montelukast Paediatric 5 mg chewable tablet should be taken once a day by mouth, as prescribed by the
doctor. Montelukast Paediatric 5 mg should be taken even when the patient has no symptoms or has an acute asthma attack. This medicine should be taken exactly as advised by the doctor or pharmacist.

Use in children and adolescents
For children 6 to 14 years of age:
One Montelukast Paediatric 5 mg chewable tablet is to be taken daily in the evening. Montelukast Paediatric 5 mg should not be taken immediately with food; it should be taken at least 1 hour before or 2 hours after food.

If the patient is taking Montelukast Paediatric 5 mg, the patient or caregiver should ensure that the patient does not take any other medicines that contain the same active ingredient, montelukast.

Montelukast Paediatric 5 mg chewable tablet is not recommended in children below 6 years of age.

Montelukast Paediatric 5 mg can only be obtained on prescription.

For further information on how Montelukast Paediatric 5 mg are used, please see the Summary of Product Characteristics available on the MHRA website.

What benefits of Montelukast Paediatric 5 mg have been shown in studies?
As Montelukast Paediatric 5 mg is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Cipla (EU) Limited) has provided data from the published literature on montelukast.

What are the possible side effects of Montelukast Paediatric 5 mg?
Because Montelukast Paediatric 5 mg is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why is Montelukast Paediatric 5 mg approved?
It was concluded that, in accordance with EU requirements, Montelukast Paediatric 5 mg has been shown to have comparable quality and to be bioequivalent to Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK). Therefore, the view was that, as for Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK), the benefits of Montelukast Paediatric 5 mg are greater than its risks and it was recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Montelukast Paediatric 5 mg?
A Risk Management Plan has been developed to ensure that Montelukast Paediatric 5 mg is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Montelukast Paediatric 5 mg approved, 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 Montelukast Paediatric 5 mg.
Bulgaria, Cyprus, Czech Republic, Hungary, Ireland, Malta, Romania, Slovenia, Slovak Republic and the UK agreed to grant a Marketing Authorisation for Montelukast Paediatric 5 mg on 01 July 2014. A Marketing Authorisation was granted in the UK on 30 July 2014.

The full PAR for Montelukast Paediatric 5 mg follows this summary.

For more information about treatment with Montelukast Paediatric 5 mg, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2014.
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## Module 1

### Information about the initial procedure

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<th>Product Name</th>
<th>Montelukast Paediatric 5 mg chewable tablets</th>
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<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<td>Active Substance</td>
<td>Montelukast sodium</td>
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<td>Form</td>
<td>Chewable tablet</td>
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<tr>
<td>Strength</td>
<td>5 mg</td>
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<td>MA Holder</td>
<td>Cipla (EU) Limited</td>
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<tr>
<td></td>
<td>Hillbrow House, Hillbrow Road,</td>
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<tr>
<td></td>
<td>Esher, Surrey, KT10 9NW, United Kingdom</td>
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<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<td>Concerned Member States (CMS)</td>
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<td>UK/H/5411/002/DC</td>
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<td>Timetable</td>
<td>End of procedure (Day 210) – 01 July 2014</td>
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Module 2
Summary of Product Characteristics

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.
Module 3
Patient Information leaflet

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.
Module 4
Labelling
Montelukast Paediatric 5 mg chewable tablets

One chewable tablet contains montelukast sodium, which is equivalent to 5 mg montelukast.

Expiry with known effect:

Apoventra (E 351)

See the leaflet for further information.

Read the package leaflet before use.

Keep out of the sight and reach of children.

Store in the original package in order to protect from light and moisture.

Affix dispensing label here.

Codex No.: XXX/000/5/000

Montelukast Paediatric

5 mg
chewable tablets

For oral use

Cipla

MA Holder: Cipla (EU) Limited,
Hillbrow House, Hillbrow Road, Esler,
Surrey, KT10 9NN, United Kingdom

PL 26300/0153
PA 1850/004/002

BARCODE

Montelukast Paediatric 5 mg chewable tablets

MA Holder: CIPLA (EU) LIMITED

EMBOSSING ZONE

Montelukast Paediatric 5 mg chewable tablets

MA Holder: CIPLA (EU) LIMITED

EMBOSSING ZONE

Montelukast Paediatric 5 mg chewable tablets

MA Holder: CIPLA (EU) LIMITED

EMBOSSING ZONE
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Montelukast Paediatric 5 mg chewable tablets (PL 36390/0153; UK/H/5411/002/DC) could be approved. The product is a prescription-only medicine (POM) indicated for patients 6 to 14 years old:

- in the treatment of asthma as add-on therapy in those patients with mild to moderate persistent asthma who are inadequately controlled on inhaled corticosteroids and in whom 'as-needed' short-acting β-agonists provide inadequate clinical control of asthma.
- as an alternative treatment option to low-dose inhaled corticosteroids for patients with mild persistent asthma who do not have a recent history of serious asthma attacks that required oral corticosteroid use, and who have demonstrated that they are not capable of using inhaled corticosteroids.
- for the prophylaxis of asthma in which the predominant component is exercise-induced bronchoconstriction.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Bulgaria, Cyprus, Czech Republic, Hungary, Ireland, Malta, Romania, Slovenia and Slovak Republic as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Singulair 5 mg tablets (Merck Sharp & Dohme, UK), which were first authorised in the UK on 15 January 1998 following a Mutual Recognition procedure with Finland RMS and the UK as a CMS.

Montelukast is a cysteinyl leukotriene antagonist. It competitively blocks the action of leukotriene D4 (and secondary ligands LTC4 and LTE4) on this receptor in the lungs and bronchial tubes. This reduces bronchoconstriction and inflammation in asthma but it has no usable effects in acute asthma attacks.

One single-dose bioequivalence study was submitted to support this application, comparing the applicant’s test product Montelukast Paediatric 5 mg chewable tablets (Cipla Limited) and the reference product Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK). The bioequivalence study report provides the statement that the study was conducted in accordance with current version of the Principles of Declaration of Helsinki (Revised Seoul, October 2008) and in compliance to the current ICH GCP, OECD GLP, National Regulations (ICMR Guidelines), Indian GCP and ‘Schedule Y’ of Indian Drugs and Cosmetics Act and European Guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

As a non-clinical literature review has been submitted, it cannot be verified whether the studies cited were conducted in compliance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

For the published references it was not possible to verify the compliance with the GCP regulations, however no reason for concern was identified during the review.
The RMS has been assured that acceptable standards of GMP are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 01 July 2014. After a subsequent national phase, a licence was granted in the UK on 30 July 2014.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Montelukast Paediatric 5 mg chewable tablets |
| Name(s) of the active substance(s) (INN) | Montelukast sodium |
| Pharmacotherapeutic classification (ATC code) | Leukotriene receptor antagonist (R03D C03) |
| Pharmaceutical form and strength(s) | Chewable tablets; 5 mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/5411/002/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Bulgaria, Cyprus, Czech Republic, Hungary, Ireland, Malta, Romania, Slovenia and Slovak Republic |
| Marketing Authorisation Number(s) | PL 36390/0153 |
| Name and address of the authorisation holder | Cipla (EU) Limited 
Hillbrow House, Hillbrow Road, 
Esher, Surrey, KT10 9NW, 
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Montelukast sodium
Chemical name: Sodium 1-[[[(1R)-1-[(3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]-phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio)methyl]cyclopropane acetic acid.

Structural formula:

Montelukast is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, microcrystalline cellulose, hydroxypropyl cellulose (E463), red iron oxide (E172), croscarmellose sodium, aspartame (E951), magnesium stearate and Cherry flavour (which contains maltodextrin (maize), nature identical flavouring substance, acacia gum (E 414), propylene glycol, flavouring preparation and natural flavouring substance).
All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of cherry flavour and red oxide red (which are compliant with suitable in-house specifications). In addition, the in-house specifications for ferric oxide red are in compliance with current EEC directives concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**
The objective of the development programme was to formulate robust, stable tablets containing 5 mg montelukast that could be considered as a generic medicinal product of Singulair Paediatric 5 mg Chewable Tablets (Merck Sharp & Dohme). 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 product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and shown satisfactory results. The Marketing Authorisation Holder (MAH) has committed to perform process validation on future commercial scale batches.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and 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.

**Container-Closure System**
The finished product is packaged in oriented polyamide polyvinylchloride (PVC)/aluminium blisters. The blisters are packaged with the Patient Information Leaflet in cartons, in pack sizes and are available in pack sizes of 10, 14, 28, 56 and 100 chewable tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011) concerning materials in contact with foodstuff.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Store in the original package in order to protect from light and moisture.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of montelukast sodium are well-known, no new non-clinical studies are required and none have been provided.

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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
The clinical pharmacology of montelukast is well-known. No new pharmacodynamic or pharmacokinetic data was required for this application.

In support of this application, the Marketing Authorisation holder has submitted the following bioequivalence study:

An open label, randomised, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study to compare the pharmacokinetics of the test product Montelukast Paediatric 5 mg chewable tablets (Cipla Limited) versus the reference product Singulair 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK) in healthy adult male and female volunteers under fasting conditions.
The subjects were administered a single dose (one 5 mg chewable tablet) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 36 hours after each administration. The washout period between the treatment phases was 4 days. The pharmacokinetic results are presented below:

### Log-transformed PK parameters for Montelukast (5mg strength)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Geometric Least Squares Mean</th>
<th>T/R %</th>
<th>Lower</th>
<th>Upper</th>
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<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
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</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>360.9625</td>
<td>345.5370</td>
<td>104.46</td>
<td>99.46</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>1852.5289</td>
<td>1867.4804</td>
<td>99.20</td>
<td>95.70</td>
</tr>
</tbody>
</table>

Cmax  maximum plasma concentration over the sampling period
AUC_{0-t}  area under the plasma concentration curve from administration to last observed concentration at time t.

The 90% confidence intervals for AUC and Cmax for test versus reference product for montelukast are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Based on the submitted bioequivalence study Montelukast Paediatric 5 mg Chewable Tablets is considered bioequivalent with Singulair Paediatric 5 mg Chewable Tablets.

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

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

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this type of application. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in line with current guidelines.

**MAA Form**
The MAA form is satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

Conclusion
There are no objections to the approval of this product from a clinical view-point.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The quality characteristics of Montelukast Paediatric 5 mg chewable tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application. The pharmacodynamic, pharmacokinetic and toxicological properties of montelukast are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Montelukast Paediatric 5 mg chewable tablets (Cipla Limited) and the reference product Singulair 5 mg Chewable Tablets (Merck Sharp & Dohme Limited, UK).

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of montelukast sodium is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with montelukast sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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