Public Assessment Report

Decentralised Procedure

Hydrocortisone 10 mg Tablets
Hydrocortisone 20 mg Tablets

(Hydrocortisone)

Procedure No: UK/H/5949/001-002/DC

UK Licence Number: PL 10321/0204-205

Resolution Chemicals Ltd.
LAY SUMMARY

Hydrocortisone 10 mg and 20 mg Tablets.

(hydrocortisone, tablet, 10 mg and 20 mg)

This is a summary of the Public Assessment Report (PAR) for Hydrocortisone 10 mg Tablets (PL 10321/0204; UK/H/5949/001/DC) and Hydrocortisone 20 mg Tablets (PL 10321/0205; UK/H/5949/002/DC). It explains how Hydrocortisone 10 mg and 20 mg 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 Hydrocortisone 10 mg and 20 mg Tablets.

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

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

What are Hydrocortisone Tablets and what are they used for?

Hydrocortisone Tablets are ‘generic medicines’. This means that Hydrocortisone Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) Limited).

Hydrocortisone Tablets are indicated

- For use as replacement therapy for children with congenital adrenal hyperplasia which affects the body’s natural production of steroids.
- To treat severe asthma and allergic reactions.

How do Hydrocortisone Tablets work?

Hydrocortisone belongs to a group of medicines called steroids. Their full name is corticosteroids. These medicines are used to replace the adrenal hormones in the patient’s body which may be lacking.

These corticosteroids occur naturally in the body, and help to maintain health and well-being. Boosting the body with extra corticosteroid (such as hydrocortisone) is an effective way to treat various illnesses involving inflammation in the body. Hydrocortisone reduces this inflammation, which could otherwise go on making the patient’s condition worse. The patient must take this medicine regularly to get maximum benefit from it.

How are Hydrocortisone Tablets used?

The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient must check with their doctor or pharmacist if they are not sure. The amount of medicine the patient has to take each day will depend on their illness.

The patient should always carry a Steroid Treatment Card. The patient must make sure their doctor or pharmacist gives them this and has filled out the details including the dose and how long the patient will have the treatment.

The number of tablets to be taken will be on the label of the patient’s medicine. If the patient is unsure
about the dose they should take, they must talk to their doctor or pharmacist. The usual doses of Hydrocortisone Tablets are:

**Dosage for acute emergencies:**
The usual dose for adults is 60-80mg every 4-6 hours for 24 hours then gradually lowering over several days.

**Use as replacement therapy in children**
When used in replacement therapy, the usual dose for children is 10-30mg divided into two doses each day. The first dose taken in the morning may be larger than the second dose taken in the evening.

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 Hydrocortisone Tablets have been shown in studies?**
Because Hydrocortisone Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) 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 Hydrocortisone Tablets?**
Because Hydrocortisone Tablets are generic medicines and are bioequivalent to the reference medicines Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) Limited), their benefits and possible side effects are taken as being the same as the reference medicines.

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

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

**Why was Hydrocortisone Tablets approved?**
It was concluded that, in accordance with EU requirements, Hydrocortisone Tablets has been shown to have comparable quality and to be bioequivalent to Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) Limited). Therefore, the MHRA decided that, as for Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) 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 Hydrocortisone Tablets?**
A risk management plan (RMP) has been developed to ensure that Hydrocortisone Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Hydrocortisone 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 Hydrocortisone Tablets**
Malta and the UK agreed to grant Marketing Authorisations for Hydrocortisone Tablets on 09 February 2016. Marketing Authorisations were granted in the UK on 01 March 2016.
The full PAR for Hydrocortisone Tablets follows this summary.

For more information about treatment with Hydrocortisone Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2016.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I  Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II  Quality aspects</td>
<td>8</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>IV  Clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>V   User consultation</td>
<td>14</td>
</tr>
<tr>
<td>VI  Overall conclusion, benefit/risk assessment and recommendation</td>
<td>15</td>
</tr>
</tbody>
</table>
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Resolution Chemicals Ltd, marketing authorisations for the medicinal products Hydrocortisone Tablets (PL 10321/0204-5; UK/H/5949/001-002/DC) The products are prescription-only medicines (POM) indicated for:

- Use as replacement therapy in congenital adrenal hyperplasia in children.
- The emergency treatment of severe bronchial asthma, drug hypersensitivity reactions, serum sickness, angioneurotic oedema and anaphylaxis in adults and children.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Malta as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Hydrocortisone 10mg and 20mg Tablets which were originally authorised to Merck, Sharp & Dohme Ltd on 23 February 1989 (PL 00025/5053R and 5054R) and underwent change of ownership procedures to Auden Mckenzie (Pharma Division) Ltd on 03 June 2008 (PL 17507/0097-0098) and to S.N.S Pharmaceuticals Limited on 27 December 2013 (PL 16876/0002-003) and to the current marketing authorisation holder Auden Mckenzie (Pharma Division) Limited on 23 January 2015 (PL 17507/0246 & 0248).

The proposed indications are not the same as the reference product. However, the proposed indications are more restrictive and all the indications proposed here are in the reference product. Further it is agreed that the proposed indications do not infringe on the indication of "Treatment of Adrenal insufficiency" granted to the Orphan medicinal product Plenadren (ViroPharma SPRL).

Hydrocortisone is a synthetic glucocorticoid (ATC classification H02A B09, adrenal corticosteroids) with a broad range of therapeutic effects, similar to cortisol, the major endogenous glucocorticoid in humans. Hydrocortisone interacts with specific intracellular receptor proteins in target tissues to alter the expression of corticosteroid-responsive genes, resulting in metabolic effects on carbohydrates, proteins and fats, including stimulation of lipolysis and protein breakdown, as well as increased gluconeogenesis. In addition, hydrocortisone, like other glucocorticoids, inhibits many events of the inflammatory and immune response by various mechanisms.

One bioequivalence study (single-dose study conducted under fasting conditions) was submitted to support these applications. The applicant has stated that the bioequivalence study was conducted in compliance with the study protocol and the following regulations: ICH E6 Guideline for Good Clinical practice (GCP), the Declaration of Helsinki as last amended and accepted by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013, Guideline on the Investigation on Bioequivalence Revision 1, Directive 2001/20/EC, Directive 2005/28/EC, OECD principles of Good Laboratory Practice (GLP), Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug products, Guidance for Industry: Bioanalytical method Validation, and national law concerning clinical trials were followed. The declaration of Helsinki was followed, as mentioned above, with the exception of the registration of the study in a public database.

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

The RMS 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, assembly and batch release of these products.

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, ‘close-out letters’ or ‘exchange of information’
issued by the inspection services of the competent authorities (or those countries with which the EEA
has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards
of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure on 09
February 2016. After a subsequent national phase, licences were granted in the UK on 01 March 2016.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 10 mg or 20 mg hydrocortisone, as the active ingredient. Other ingredients consist of the pharmaceutical excipients prosolv 90 (silicified microcrystalline cellulose), magnesium stearate, talc and sodium starch glycolate.

Hydrocortisone 10 mg and 20 mg Tablets are packaged in AquaBa® PVC/PVdC/aluminium foil blister packs containing 30 tablets. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Hydrocortisone
Chemical name: 11β, 17α, 21-trihydroxypregn-4-ene-3, 20-dione
Structure:

![Molecular structure of Hydrocortisone]

Molecular formula: \( \text{C}_{21}\text{H}_{30}\text{O}_{5} \)
Molecular weight: 362.5
Description: White to almost white, crystalline powder.
Solubility Practically insoluble in water, sparingly soluble in acetone and in ethanol (96%); slightly soluble in methylene chloride.

Hydrocortisone 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.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets containing
10 mg or 20 mg hydrocortisone per tablet, that are generic versions of the reference products Hydrocortisone 10mg and 20mg Tablets (Auden Mckenzie (Pharma Division) 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 prosolv 90 (silicified microcrystalline cellulose) which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

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 products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The process validation protocol to be followed for full-scale production batches has been provided and is satisfactory.

**Finished Product Specification**

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 24 months with the storage condition, ‘Do not store above 25°C. Store in the original package in order to protect from light.’

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 hydrocortisone 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 Hydrocortisone 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
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

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 hydrocortisone is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 hydrocortisone.

Based on the data provided, Hydrocortisone Tablets can be considered bioequivalent to Hydrocortisone 20mg Tablets (Auden Mckenzie (Pharma Division) Limited).

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

STUDY
An open-label, randomised, single-dose, two-period, crossover, oral bioequivalence study of the applicant’s test product Hydrocortisone 20 mg Tablets (Resolution Chemicals Ltd) versus the reference product Hydrocortisone 20mg Tablets (Auden Mckenzie (Pharma Division) Limited) in healthy, adult, subjects under fasting conditions.
The subjects were administered a single dose (20 mg) of either the test or the reference product under fasting conditions. A single dose of 4 mg dose of dexamethasone was administered at least 10 hours prior to investigational product administration to suppress endogenous cortisol secretion.

Blood samples were collected for plasma levels before dosing and up to and including 12 hours after each administration. The washout period between the treatment phases was 1 day. The pharmacokinetic results are presented below:

**Table: Pharmacokinetic parameters for hydrocortisone:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEST</th>
<th>REFERENCE</th>
<th>RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>MEAN</td>
<td>CV (%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt; (ng·h/mL)</td>
<td>1034.0</td>
<td>1015.2</td>
<td>18.88</td>
</tr>
<tr>
<td>ln(AUC&lt;sub&gt;(0-t)&lt;/sub&gt;) (ng·h/mL)</td>
<td>1016.2</td>
<td>990.6</td>
<td>2.76</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt; (ng·h/mL)</td>
<td>1073.7</td>
<td>1051.8</td>
<td>18.47</td>
</tr>
<tr>
<td>ln(AUC&lt;sub&gt;(0-∞)&lt;/sub&gt;) (ng·h/mL)</td>
<td>1056.1</td>
<td>1028.2</td>
<td>2.67</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>301.8</td>
<td>295.9</td>
<td>16.09</td>
</tr>
<tr>
<td>ln(C&lt;sub&gt;max&lt;/sub&gt;) (ng/mL)</td>
<td>298.0</td>
<td>293.2</td>
<td>2.88</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.89</td>
<td>0.77</td>
<td>46.62</td>
</tr>
<tr>
<td>λ&lt;sub&gt;d&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.43183</td>
<td>0.46363</td>
<td>16.44</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.65</td>
<td>1.59</td>
<td>15.94</td>
</tr>
</tbody>
</table>

AUC<sub>(0-t)</sub> area under the plasma concentration-time curve from zero to t hours
AUC<sub>(0-∞)</sub> area under the plasma concentration-time curve from time zero to infinity
C<sub>max</sub> maximum plasma concentration

**Table: Summary of comparative bioequivalence data and 90% Confidence Interval (CI) for hydrocortisone:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>T</th>
<th>R</th>
<th>RATIO</th>
<th>90% CONFIDENCE LIMITS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt; (ng·h/mL)</td>
<td>1016.2</td>
<td>990.6</td>
<td>102.57</td>
<td>99.55-105.70</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>298.0</td>
<td>293.2</td>
<td>101.65</td>
<td>97.55-105.93</td>
</tr>
</tbody>
</table>
Conclusion

The 90% confidence intervals of the test/reference ratio for AUC, and $C_{\text{max}}$ values for hydrocortisone for the 20 mg strength 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 Hydrocortisone 20mg Tablets (Auden Mckenzie (Pharma Division) Limited).

As the 10 mg and 20 mg strength test products meet the biowaiver criteria specified in the current bioequivalence guidance, the results and conclusions of the bioequivalence study with the 20 mg tablet strength can be extrapolated to the 10 mg strength tablet.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

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

IV.5 Clinical safety

No new safety data were submitted and none are required.

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 Hydrocortisone Tablets.

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

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th></th>
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<tbody>
<tr>
<td>• Hypersensitivity to the drug product or any of the excipients</td>
<td></td>
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<tr>
<td>• New infections and/or increase in susceptibility to infections and their severity</td>
<td></td>
</tr>
<tr>
<td>• Impairment of immune response and risk of viraemia in patients vaccinated with live viral vaccines</td>
<td></td>
</tr>
<tr>
<td>• Development of adrenal cortical atrophy on prolonged therapy</td>
<td></td>
</tr>
<tr>
<td>• Risk of growth retardation in infancy, childhood and adolescence</td>
<td></td>
</tr>
<tr>
<td>• Antagonism of effects of hypoglycaemic drugs (including insulin), anti-hypertensives and diuretics on concomitant use with corticosteroids</td>
<td></td>
</tr>
<tr>
<td>• Increased risk of GI bleeding and ulceration with concomitant use of salicylates or NSAIDs</td>
<td></td>
</tr>
<tr>
<td>• Risk of hypokalaemia with concomitant use of acetazolamide, loop diuretics, thiazide diuretics, carbonic anhydrase inhibitors, theophylline, amphotericin and sympathomimetics</td>
<td></td>
</tr>
<tr>
<td>• Risk of congenital abnormalities and intra-uterine growth retardation via transplacental exposure</td>
<td></td>
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<tr>
<td>• Withdrawal symptoms after abrupt discontinuation of treatment</td>
<td></td>
</tr>
<tr>
<td>• Use in patients with underlying conditions (osteoporosis, hypertension or congestive heart failure, existing or previous history of severe affective disorders, diabetes mellitus, previous history of tuberculosis or characteristic appearance on a chest x-ray, glaucoma,</td>
<td></td>
</tr>
</tbody>
</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s test product Hydrocortisone 20 mg Tablets (Resolution Chemicals Ltd) and the reference product Hydrocortisone 20mg Tablets (Auden Mckenzie (Pharma Division) Limited).

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 package leaflet 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 products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with hydrocortisone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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 Hydrocortisone Tablets is presented below: