Development of a Novel Paediatric Belumosudil Oral Suspension

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PURPOSE

Belumosudil, a ROCK2 selective inhibitor, is currently in development for the treatment of immune disorders. A formulation was required suitable for a paediatric patient population aged between three months and twelve years. The aim of this development programme was to develop a suitable, novel belumosudil oral suspension formulation using age-appropriate excipients to be used in a relative bioavailability assessment of the suspension compared to the reference adult tablet formulation. A liquid formulation enables flexible dosing by varying the dose volume according to the age and/or body weight of the patient.

METHODS

The design of the formulation and selection of excipients were based on literature reviews including review of the FDA Inactive Ingredients Database[2], STEP Database[3] and guidance provided by the European Medicines Agency (EMA)[4] including assessment of ADIs and precedence of use in the target age range for each excipient.

Formulations were assessed with combinations of suspending/thickening agents, preservative, sweetener and flavours to identify the most promising systems. Lead flavour and sweetener combinations that showed improved palatability when compared to the unflavoured/unsweetened control system were identified from a human volunteer taste study[5] and development activities were performed to optimise the thickener/suspending system for belumosudil.

An assessment of jet-milled and pin-milled belumosudil was carried out to select the most appropriate input material for use in the oral suspension. Three prototypes were identified from the development programme and a lead formulation was selected following short-term stability testing.

Process development studies were conducted to allow the scale up of the formulation for clinical trial material (CTM) manufacture.

CONCLUSIONS

There was a requirement for the development of a paediatric formulation for the treatment of immune disorders in the paediatric population.

Reviews of literature and regulatory guidance, selection of age-appropriate excipients at optimal levels of inclusion and process development work allowed the development of a 40mg/ml Belumosudil Oral Suspension.

This suspension is suitable for children from 3 months to 12 years and manufactured to a scale of up to 2.6L for CTM manufacture for use in a relative bioavailability assessment to compare with the reference adult formulation.

RESULTS

The outcome of the development programme resulted in the successful identification of a 40 mg/ml Belumosudil Oral Suspension in line with the QTPP. The development work identified some physical instability with alternative viscosity modifiers and suspending agents and confirmed a PVP / colloidal silica system at suitable levels of inclusion for the paediatric population which demonstrated satisfactory dispersion and resuspendability of the API.

A comparison of formulations manufactured with the alternative milling technologies for belumosudil resulted in the selection of jet-milled API as the preferred form for achieving uniform homogeneity and meeting the QTPP.

Chemical and physical stability was demonstrated at accelerated storage conditions and complete dissolution of the API using a USP II dissolution apparatus was achieved, with >90% dissolved after 5 minutes.

Process development to confirm the critical process parameters allowed the successful scale-up from 100ml to 2.6L with satisfactory bulk homogeneity.

Quality Attribute	Target
Dosage form	Oral Suspension
Active pharmaceutical ingredient (API) concentration	40 mg/ml
Assay	90.0% - 110.0%
Microbiological Limits	Meets pharmacopoeial acceptance criteria
Visual Appearance	Uniform colour

Table 1. QTPP for a Novel Paediatric Belumosudil Oral Suspension

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